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"Development of a Computer Decision Support System for Women with BRCA1 or BRCA2 Mutations" is a project that aims to develop a decision support system that provides individualized information about the expected benefits of alternative cancer risk reductions strategies for women with either a BRCA1 or BRCA1 mutation. Many valuable steps have been taken in the second year of this grant, including the development of the educational booklet, the layout of the decision aid, the completion of the decision support system, and the protocol for the randomized control trial. All of the elements are in place for the randomized control trial to begin. Although delayed somewhat by the complexities of the computerized decision support system, enrollment for the randomized control trial will begin on August 1, 2000.

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Katrina Arroyo 7/28/00

PI - Signature Date

# Table of Contents

**Appendix J:** "Factors associated with decisions about clinical BRCA1/2 testing"

**Appendix K:** "Postmenopausal Hormone Replacement Therapy in Women with Hereditary Breast Cancer Susceptibility: A Decision Analysis"

**Appendix L:** "Comprehension of Survival Curves by the General Public"

**Appendix M:** "Breast Cancer Risk Perception and Use of Postmenopausal Hormone Replacement Therapy"

## Introduction

"Development of a Computer Decision Support System for Women with BRCA1 or BRCA2 Mutations" is a project that aims to develop a decision support system that provides individualized information about the expected benefits of alternative cancer risk reduction strategies for women with either a BRCA1 or BRCA2 mutation. For decision making about cancer risk reduction by women with BRCA1 or BRCA2 mutations to be truly informed, decisions must be consistent with a woman's personal preferences and values. Such decisions ultimately can only be made by the woman involved - she is the only one able to adequately value the trade-offs among the benefits, risks, and costs of the alternative management strategies. The objective of this project is to develop and evaluate a Decision Support System (DSS) that will improve informed decision making by providing women with tailored, simplified information about the expected health outcomes of alternative decisions. Based on a Markov model, the proposed DSS will be easily updated with new epidemiological evidence to provide women with the most accurate and up to date information about their risk and expected outcomes. While the DSS will use the advantages of a web-based interface, the individualized information generated by the Markov model simulations will be printed out and sent home with the woman to review with family members and friends, if she wishes. Thus, the proposed DSS will be a powerful, accessible and critically needed tool to improve patient decisions and health outcomes among women with BRCA1 and BRCA2 mutations.

## Body

Phase One: Development of Educational Booklet

Using the information gathered through several focus groups conducted from the Fall of 1998 through the Spring of 1999, the educational booklet was written and illustrated. Entitled "Health Care Options for Women at Risk for Breast and Ovarian Cancer," the booklet covers topics suggested by women who have either been counseled about being tested or have been tested for a BRCA1 or BRCA2 mutation. The illustrations completed by a medical illustrator at the University of Pennsylvania complement the text and aide in the understanding of the results of prophylactic surgeries. Drafts of the booklet were critically reviewed several times by an expert panel including Barbara Weber, MD, Andrea Eisen, MD, Jill Stopfer, MS and Kathleen Calzone, M.S.N. Importantly these reviews led to the addition of several sections including breast and ovarian cancer screening, hysterectomy, and implications for family members. Currently the booklet is undergoing review by women seen at the Cancer Risk Evaluation Program in the prior 24 months to obtain suggestions and revisions from a group of women who represent the target audience, the CREP population. The women will receive the booklet in the mail and will be called one week later to review suggestions for the booklet in both content and layout. Topics that will be covered include whether the content was informative and useful, to note words, phrases or presentations they found confusing, and to identify important omissions. Once this is completed, the booklet will be revised if necessary, and published. The current draft of the booklet is attached as Appendix A.

Phase Two: Development of the Decision Support System

Part A: Development of Decision Analytic Model

The decision analytic model has been completed. Important revisions included:

1. Because the majority of women who are found to carry a mutation in BRCA1 or BRCA2 have been previously diagnosed with breast cancer and these women still face many of the same decisions about cancer risk reduction as women without a cancer diagnosis (e.g. prophylactic surgery), the investigator team felt it was important to include women with a prior diagnosis of breast cancer in the trial. Thus, we substantially revised the model to allow tailoring to the presence or absence of a previous diagnosis of breast cancer. Because survival following a diagnosis of breast cancer depends upon the characteristics of the cancer (in particular, stage and node status), we developed individual survival functions for Stage 1 and Stage 2 node positive and node negative breast cancer, further tailoring the model simulations for women with a prior diagnosis to the characteristics of their individual tumors.
2. To allow inclusion of women with a prior diagnosis of coronary heart disease and osteoporosis in the trial, we revised the model to allow simulations to be tailored to these prior diagnoses.
3. Because focus groups of women from CREP, the investigator team and expert panel all felt that showing the effect of alternative management strategies on breast cancer incidence was necessary to help women make decisions about cancer risk reduction strategies, we revised the model to allow accurate calculation of cumulative incidence curves for breast and ovarian cancer. To minimize information overload, we are currently planning to show women only the curves for overall mortality and breast cancer incidence, but allow women to request curves for ovarian cancer incidence if desired.
4. We have validated the model by comparing the estimated life expectancy from the simulation model using population based incidence rates for breast and ovarian cancer with data from the

National Center for Health Statistics. The life expectancy of a 50 year old woman at average cardiac risk who selects no therapy from the simulation is 31.68 years compared to 31.70 years estimated by the National Center for Health Statistics.

Part B: Format Effects

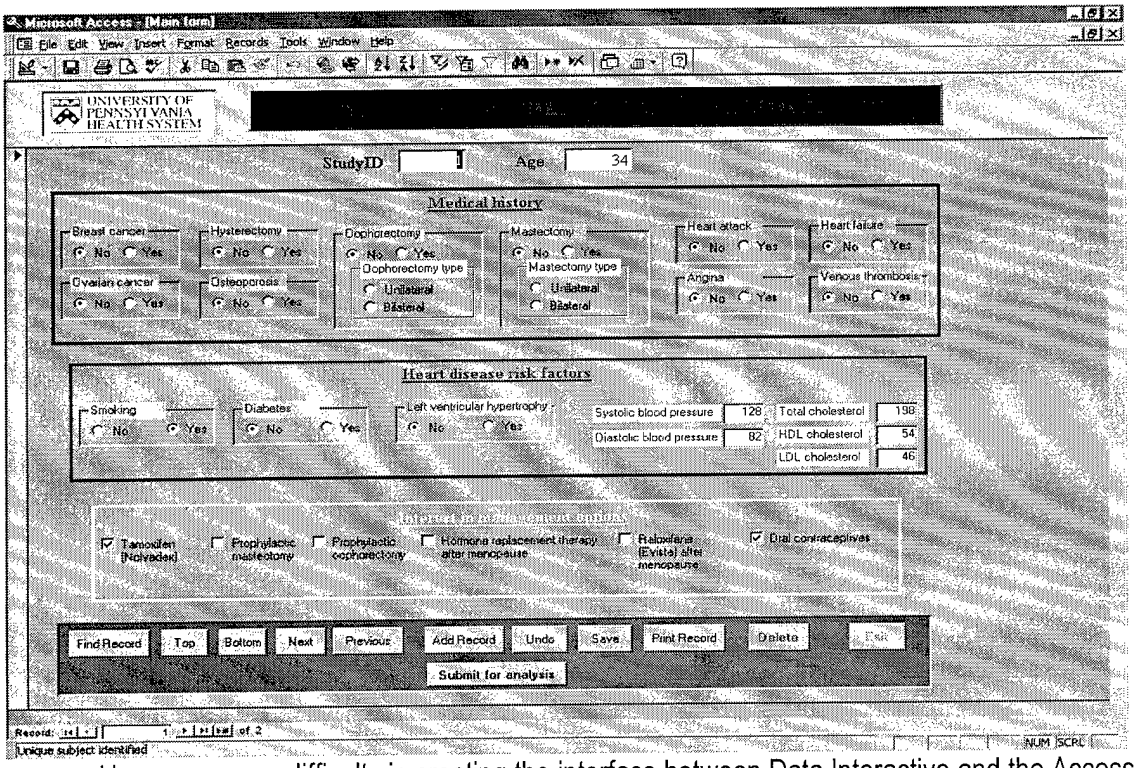
Using the data from the surveys conducted last year, the survival curve materials have been adapted to the specific context relevant to women with BRCA mutations. This involved developing text that explains the concept of survival curves and how they should be interpreted. In order for the curves to be clear and organized, we developed a method of presenting the curves that allows each woman to see her options individually as well as together.

Each decision aid includes treatment option information as well as breast cancer incidence information. A baseline (no intervention) survival curve is fixed to a divider while the treatment options, each printed on transparencies, can be superimposed over the baseline curve. This layering effect allows the women to see the difference in survival between having no treatment (baseline) and the various treatment options, which can also be compared to each other. This method enables women to clearly distinguish which option gives her the best survival rate over time.

Part C: Continued Development of the Computer Interface

Over the past 12 months, the design and function of the computer interface for the decision support system has been refined. This process has required numerous meetings with project staff and with a focus group of nurses who have an interest in breast cancer research. After numerous iterations, a final design has been implemented in Microsoft Access (shown below in the figure). The original platform (FoxPro) was abandoned this year, owing to difficulties with the transition to a client-server implementation that is expected in the future. The Access

implementation will allow a seamless transition to a Web-based platform, although the focus now is on a single, standalone system. In addition, Access supports ActiveX objects through its extensive data model, and interfaces with the Data Interactive product from TreeAge Software. The interface for this system is shown below:




However, some difficulty in creating the interface between Data Interactive and the Access application has been encountered, forcing us to develop another system in parallel, so as not to delay the project. This second system provides an interface to the Markov model in DATA, using the interface builder in DATA software. While not ideal, in that it is not particularly attractive nor does it support most of the usual Windows objects (such as buttons and panes), this second system will be used in place of the final software until the latter is fully implemented and debugged. The investigators are working with TreeAge to expedite the implementation of the Access-based system. Meanwhile, the second, simpler system has been tested and debugged, and has passed the scrutiny of the investigators and the focus group of nurses discussed above. It is now ready for deployment in the field. The documentation for the second system is included as Appendix B.

Phase Three: Randomized Controlled Trial of Patient Decision Support System

The Randomized Control Trial (RCT) is currently in the early stages. All of the questionnaires necessary for this phase have been developed, including the patient risk factor questionnaire, the baseline questionnaire, and the outcome questionnaire. The RCT is scheduled to begin on August 1, 2000, with the recruitment of all eligible subjects through the CREP, who will be randomized to receive either the educational booklet alone or the booklet along with their CDSS participation. Each woman will complete a risk factor questionnaire, which will be used to complete the CDSS for those randomized to this arm of the study.

Beginning on August 1, 2000, a member of the research staff will ensure that all new patients coming in to CREP on their initial visit receive a letter introducing them to the study (Appendix C). This is done at this point in order to tell the women what the study is about without overwhelming her at the time that she receives her testing results. Women returning for a second visit who are found eligible to be tested and would like to do so have their blood drawn. These women are asked if they would like to participate in the study, and if they agree, the research staff proceeds with informed consent. There is no standard time period between the first and second visit, therefore, the research staff will monitor the patient list on a weekly basis and go to the clinic when women are returning to have blood drawn for their test.

When a woman returns for her results disclosure, the research staff will see the women who have agreed to participate and have a BRCA1 or BRCA2 mutation, making them eligible to participate. These women are randomized at this point to either receive the booklet alone or the booklet and the individual decision aid. They are all given the educational booklet and questionnaire, "Assessment of Risk Factors & Interest in Risk Reduction Options." (Appendix D) This is completed and returned before the woman leaves. This questionnaire provides baseline

information about the woman's attitude toward her treatment options and her risk factors that are to be used in generating her decision aid if applicable. A research visit is scheduled by the research staff to review the booklet and the CDSS results with all participating women. Between visit three and the research visit, the decision aid is generated, if applicable, and a copy is given to the clinical staff and kept in a locked file.

During the research visit, the "Baseline Questionnaire" (Appendix E) is administered at the beginning of the visit. This questionnaire measures the subject's stage in the decision process, level of cancer anxiety, and depression. Using a standard script, the booklet is reviewed with both of the arms of the study. Questions that the subject may have are answered using standard guidelines, with the suggestion that any further questions be asked of the faculty of CREP. The arm receiving only the booklet gets no further information, while the decision aid group will continue. Women randomized to the decision aid will then receive their individualized aid that has been developed prior to the session. Using a script, a member of the research staff will review the decision aid with the woman to ensure that she understands what the curves show her. She will also receive a simplified copy of the decision tree to show her how these probabilities were generated. Any questions that the subject may have will be answered according to set guidelines, and any additional questions will be directed to a physician.

To measure the outcomes of the trial, each woman who participates in the RCT will receive a follow up call one month later from an assistant blinded to which arm the woman is enrolled. The questionnaire "Outcomes of Women's Health Study" (Appendix F) will be used to gather information about the woman's decisions after the trial. Outcomes will include: satisfaction with decision making, level of knowledge about decision alternatives, management decision made, and cancer anxiety and depression.

## Key Research Accomplishments

CDSS Development

- Development of Markov decision model is completed.
- Format of survival and incidence curves which women will receive as output of CDSS determined.
- Linking of CDSS to DATA output is completed.
- CDSS has been piloted by nurses/research staff and approved.

Booklet Development

- Booklet written.
- Illustrations completed.
- Currently under review with CREP patients for their input.

Randomized Control Trial

- Decision Aid contents and layout completed.
- Booklet completed. Under review by CREP patients.
- Questionnaires completed.
- Script for research visit completed.
- Protocol for RCT approved and ready to begin August 1, 2000.

## Reportable Outcomes

Published Manuscripts

- Armstrong K, FitzGerald G, Schwartz SJ, Ubel PA. Using survival curve comparisons to inform patient decision making: Can a training exercise improve understanding? Manuscript under review (Appendix G)
- Armstrong K, Eisen A, Weber BL. Assessing the Risk of Breast Cancer. N Engl J Med, 2000;324(8):564-71 (Appendix H)
- Armstrong K, Popik S, Guerra C, Ubel PA. Beliefs about breast cancer risk and use of postmenopausal hormone replacement therapy. Med Decis Making 2000(3);20:308-313 (Appendix I)
- Armstrong K, Calzone K, Stopfer J, FitzGerald G, Coyne J, Weber B. Factors associated with decisions about clinical BRCA1/2 testing. Cancer Epidemiol Biomarkers Prev, in press (Appendix J)
- Armstrong KA, Berlin M, Weber B, Schwartz JS. Postmenopausal Hormone Replacement Therapy in Women with Hereditary Breast Cancer Susceptibility: A Decision Analysis Manuscript under review (Appendix K)

Abstracts

- Armstrong K, Schwartz JS, FitzGerald GC, Ubel PA. Comprehension of Survival Curves by the General Public. Med Decis Making (Abstract) 1999;19(4):527 (Appendix L)
- Armstrong, K, Popik S, Ubel PA. Breast Cancer Risk Perception and Use of Postmenopausal Hormone Replacement Therapy. J Gen Intern Med, (Abstract) 1999;14(2):7 (Appendix M)

## Conclusions

The past year has been productive and informative. Due to unseen complications with the software that we are using to implement the model, we have had to change the approach and structure of the DSS. This has caused delays to the start of the RCT that were not anticipated. Much progress has been made, however, with the booklet, the decision aid, and the protocol for the RCT. Because these steps are completed and in place, the RCT is ready to begin on August 1, 2000.

The booklet has been written and illustrated, modified and improved upon by a panel of medical experts in the field of BRCA1 and BRCA2. The booklet is being reviewed by current CREP patients for their input, which will be incorporated into the final version of the booklet. The decision aid also underwent many improvements, and should also serve as a helpful aid for these women. With the beginning of the RCT, a new phase of the study will commence, which is both an exciting and welcome new step. The work of the past two years will be implemented, and new data will be gathered. It is hoped that the RCT produces useful information for both the patients and investigators.

# Table of Contents

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## Appendix A:
## "Health Care Options for Women at Risk for Breast and Ovarian Cancer"

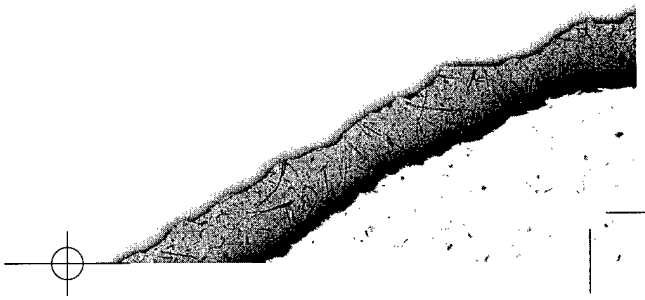
# Health Care Options for Women at Risk for Breast and Ovarian Cancer

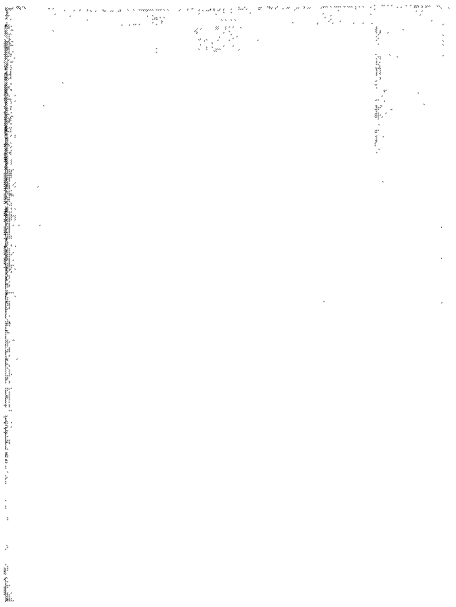
## INTRODUCTION

This booklet was developed to help women with a BRCA1 or BRCA2 mutation make decisions about how to manage their risk of breast and ovarian cancer. The goal of the booklet is to provide information about all of the options available for managing breast and ovarian cancer risk as well as other issues related to carrying a mutation in BRCA1 or BRCA2. Because these decisions are complex and each woman's situation is different, each woman should discuss her personal situation with a physician, nurse, or genetic counselor who is knowledgeable about BRCA1 and BRCA2 as well as her regular health care provider. Above all, it is important that each woman makes an informed decision.

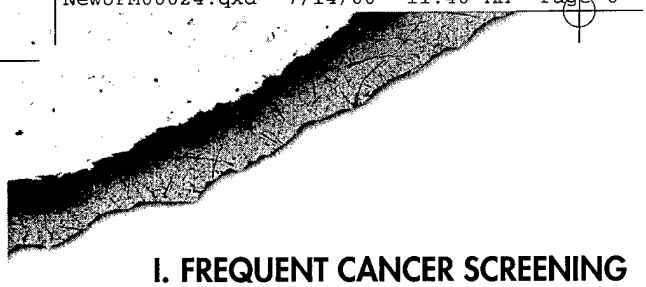
There are six sections in this booklet. Frequent breast and ovarian cancer screening is recommended for all women with a BRCA1 or BRCA2 mutation and is discussed in the first section of the booklet. The second section discusses prophylactic surgery – removal of the ovaries or the breasts prior to the development of cancer. Tamoxifen (Nolvadex), the only medication currently approved to reduce the risk of breast cancer, and oral contraceptives, which may reduce the risk of ovarian cancer, are discussed in the third section. The fourth section focuses on hormone replacement therapy and raloxifene (Evista), medications that are often considered at the time of menopause. The fifth section reviews the current knowledge about the effect of lifestyle, such as diet and exercise, on risk of breast and ovarian cancer. The last section discusses other implications of carrying a BRCA1 or BRCA2 mutation, including implications for family, insurance and confidentiality.

Because medical research moves quickly, new options for managing cancer risk may become available at any time. Regular contact with health care providers and specialized counseling programs, such as the Cancer Risk Evaluation Program, can help women with BRCA1 or BRCA2 mutations stay informed of the latest developments.





# Table of Contents



## I. FREQUENT CANCER SCREENING

The benefits of screening procedures for women with BRCA mutations have yet to be proven, and so far are based mostly on expert opinion. The types of studies needed to prove the benefits of these screening procedures may take years to become available, since researchers need to be able to follow women over time to see how these procedures affect long term outcomes. Since BRCA1 and BRCA2 were only discovered in 1994 and 1995, follow-up time for women with mutations has been limited. However, the screening recommendations are based on the known importance of early detection for cancer and what is known about individuals at average risk. Generally, cancer that is detected in earlier stages is more easily treated, and the likelihood of a cure is higher in these cases.

### Breast Cancer Screening:

### *Breast Examination*

- What is it?

Breast examination is a type of screening that involves either a woman checking her own breasts for lumps (self breast examination, or SBE), or a health care provider checking a woman's breasts for lumps (clinical breast examination, or CBE). These two types of screening are both important in the detection of changes in the breast that may be cancer. By examining her breasts once a month, a woman is likely to become very familiar with her breast contours, increasing the likelihood that she could detect a lump or other change in her breast. Health care providers are specially trained in breast examination and may be able to detect changes or lumps that cannot be felt by the woman herself.

- Who should have breast examinations?

Beginning at age 40, every woman at average risk should examine her breasts once a month for any changes in the breast, such as lumps, asymmetry, and skin changes, and have her breasts examined by her health care provider once a year. Women with a BRCA1 or BRCA2 mutation should begin breast examination at age 25.

• What are the benefits of breast examination?

Breast examination can detect lumps and other changes that may turn out to be early breast cancer. By finding cancer early it may be more easily treated and more likely to be cured. Because most studies of breast cancer screening have studied the combined effect of breast examination and mammography, it is hard to be sure exactly how much breast examination alone reduces a woman's chance of dying from breast cancer. However, most experts believe that self breast examination and clinical breast examination are important parts of breast cancer screening.

• What are the disadvantages of breast examination?

Because it is a painless, simple screening method, there are few risks associated with this type of screening. However, most lumps or other problems found by women or physicians that require evaluation are not cancer. Thus, women may undergo tests and surgeries that may be frightening and do not directly lead to a reduction in the risk of dying of breast cancer.

## *Mammography*

• What is it?

A mammogram is a x-ray of the breasts that detects abnormalities in the breast tissue.

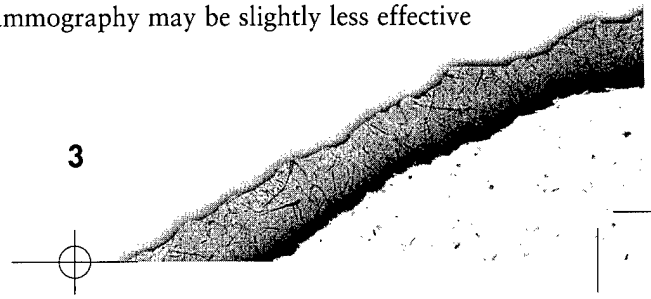
• Who has mammography?

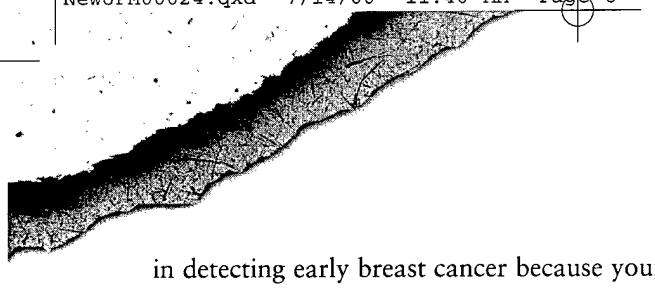
For women of average risk, it is recommended that women over 40 undergo mammography screening once a year. For women who have a BRCA mutation, it is recommended that annual mammography screening begin at age 25.

• What are the benefits of mammography?

A mammogram provides a picture of the breast that can show changes or abnormalities in the breast tissue. In some cases, this allows mammography to detect early breast cancer, before it causes any symptoms. If breast cancer is found early, it is more likely to be curable.

For women between the ages of 50 and 69, mammography reduces the chance of dying from breast cancer by as much as 30 to 50%. For women between the ages of 40 and 49, mammography may be slightly less effective





in detecting early breast cancer because younger women generally have more dense breasts. However, even in this younger age group, mammography appears to reduce the risk of dying from breast cancer by almost 25%. Furthermore, the benefits of mammography may be even greater in women at increased risk of breast cancer, such as women with a BRCA1 or BRCA2 mutation.

- What are the disadvantages of mammography?

There is some concern that beginning mammography screening between the ages of 25 and 35 could slightly increase a woman's risk for developing breast cancer from repeated exposure to radiation. Although this is a concern to be taken into account, the risk of radiation exposure through mammograms is very small. The benefits of early detection of breast cancer in a high risk woman greatly outweigh the possible risk of minimal radiation exposure.

As with breast examination, most abnormalities seen on a mammogram turn out not to be breast cancer at all. While it is always a relief to find out an abnormality is not cancer, having to undergo an evaluation can be unpleasant and cause some anxiety. This necessary evaluation of abnormal mammograms also leads to breast biopsies and other tests that may not have happened if the mammogram had not been done.

### *MRI*

- What is it?

Breast MRI (Magnetic Resonance Imaging) uses the interaction between magnets and radio waves to produce cross-sectional pictures of the breast that are much more detailed than mammography. Its usefulness in screening women at high risk for breast cancer is currently under study.

- Who has breast MRI?

Breast MRI is not currently recommended as routine breast cancer screening for any group of women. However, women who are at high risk for breast cancer may be eligible to participate in research studies of breast MRI. Women who are pregnant, or have a pacemaker or any surgically implanted metal device, are not eligible for an MRI.

• What are the benefits of breast MRI?

Breast MRI gives a more detailed picture of the breast than a mammogram. This more detailed picture allows MRI to detect some early breast cancers that are not found by mammography. This technique is currently being investigated as a screening tool for high risk women.

• What are the disadvantages of breast MRI?

Breast MRI does not have any major side effects. Because the imaging requires that the woman lie completely still during the thirty to forty minute process, it can be a slightly uncomfortable experience, especially if a woman is claustrophobic. Breast MRI may also detect abnormalities that are not cancer – leading to breast biopsies and other tests that may not have happened if the MRI had not been done. The balance between the risk of these biopsies and the ability of the MRI to find early cancer is not yet known.

## OVARIAN CANCER SCREENING:

### *Pelvic Examination*

• What is a pelvic examination?

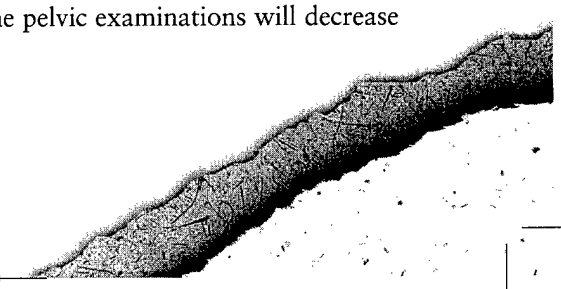
A pelvic exam involves a health care provider examining a woman's cervix, uterus and ovaries with an internal exam. It usually involves two parts: (1) a speculum examination where samples are taken from the cervix; and (2) bimanual examination where the uterus and ovaries are felt with a hand in the vagina. Because the ovaries can be felt at the time of a bimanual examination, a pelvic examination is sometimes considered one part of ovarian cancer screening.

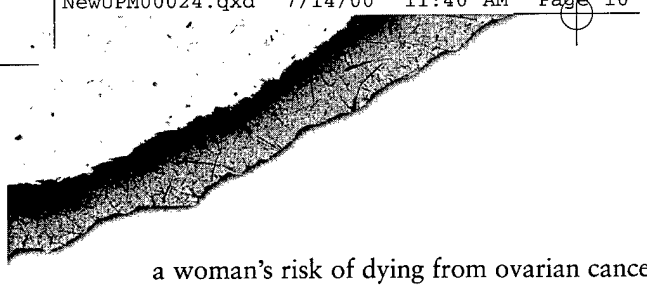
• Who has a pelvic exam?

Any woman over the age of 18 or who is sexually active should have a pelvic exam once a year.

• What are the benefits of a pelvic exam?

A pelvic exam may detect changes in the ovaries that may represent early ovarian cancer. If ovarian cancers are found early, they may be more easily treated and more likely to be cured. However, because the ovaries are difficult to feel, pelvic examination misses many early ovarian cancers. Currently, there are no studies that suggest that routine pelvic examinations will decrease





a woman's risk of dying from ovarian cancer. However, PAP smears, which are done at the time of the speculum examination, are very important in reducing a woman's risk of dying from cervical cancer. Thus, it is reasonable to recommend annual pelvic examinations for all women.

- What are the disadvantages of this screening?

There are no major side effects to this type of screening. The major disadvantage to this screening is that it is not a very effective way to detect ovarian cancer, and some women find the procedure embarrassing or uncomfortable.

### *CA-125 and Trans-Vaginal Ultrasound of the Ovaries*

- What are they?

These are tests that are often conducted together in order to detect early ovarian cancer in high-risk women. The CA-125 test is a blood test that measures the levels of a protein made by some ovarian cancers. A vaginal ultrasound produces pictures of the ovaries by inserting a small ultrasound probe into the vagina.

- Who has this screening?

Women who are at an increased risk for ovarian cancer, such as women with a BRCA1 or BRCA2 mutation, may begin to get an annual or biannual CA-125 test and ultrasound as early as age 25.

- What are the benefits of this screening?

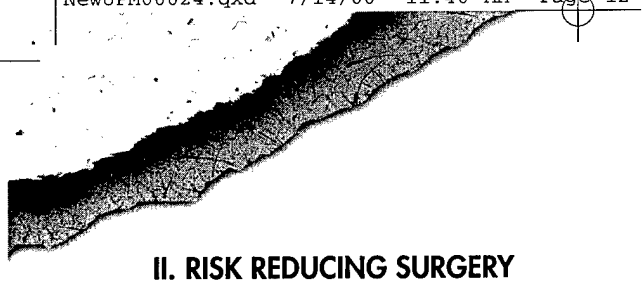
CA-125 is present in low levels in the body at all times, but can become elevated with reproductive system cancers, such as ovarian cancer. Because the CA-125 test may detect the presence of ovarian cancer before a woman experiences any symptoms, CA-125 screening may catch ovarian cancer at an earlier stage when it is more likely to be curable.

By producing images of the ovaries, vaginal ultrasound may detect early ovarian cancer. Experts believe the tests in combination are better at detecting ovarian cancer than either test alone. Although there currently is no data showing that CA-125 test and vaginal ultrasound will reduce the chance of

dying from ovarian cancer, the tests are relatively simple and painless. Thus, many women at high risk for developing ovarian cancer may wish to undergo these tests even in the absence of proven benefit if they are not yet ready to consider surgical removal of the ovaries.

- What are the disadvantages of this screening?

A CA-125 test does not test exclusively for ovarian cancer. An elevated CA-125 level may indicate a number of conditions, including menstruation, pregnancy, and ovarian cysts. Furthermore, CA-125 levels do not always rise in the early stages of ovarian cancer, meaning a woman may have early stage ovarian cancer and a normal CA-125 level. Vaginal ultrasound may also miss early ovarian cancers and detect many abnormalities that do not turn out be cancer. Because these tests frequently miss early ovarian cancers, it is not clear that they will significantly reduce a woman's risk of dying of ovarian cancer. Because these tests may pick up abnormalities that are not ovarian cancer, women may undergo extra tests and even surgeries to evaluate these abnormalities. These extra tests can be unpleasant and anxiety producing and probably would not have been needed if the screening tests had not been done.



## II. RISK REDUCING SURGERY

Prophylactic surgery involves the removal of healthy tissue, such as the breasts or ovaries, in order to decrease the risk of developing cancer.

### *Prophylactic Oophorectomy*

- What is a prophylactic oophorectomy?

Prophylactic oophorectomy is the surgical removal of both ovaries before there is any sign of ovarian cancer to decrease the chance of developing ovarian cancer.

- How is a prophylactic oophorectomy performed?

A prophylactic oophorectomy is an operation that often can be performed through a laparascope (a thin, pencil-like instrument). If the oophorectomy is done with a laparascope, it usually does not require a hospital stay. Preoperative tests are conducted on an outpatient basis. After not eating or drinking anything for several hours, a woman is given general anesthesia. During this time, she is asleep and cannot feel pain. A gas is pumped into the abdomen to give the surgeon space to operate safely. The laparoscope is inserted into the abdomen through a small incision just below the navel through which the ovaries are removed. Most women go home the same day as the operation. After a few days of mild abdominal discomfort, most women return to their normal activities, and are fully recovered in less than two weeks.

Occasionally a prophylactic oophorectomy will require an open surgery, especially if the uterus is removed at the same time (hysterectomy) or if a woman has had previous abdominal surgery. Therefore, a consultation with a gynecological oncologist is recommended. If an open surgery is necessary, the woman will stay in the hospital for several days after the surgery and will recover fully in four to six weeks.

- What are the benefits of a prophylactic oophorectomy?

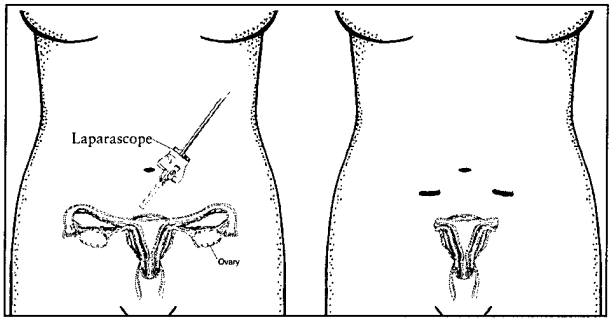
At present, there is only preliminary information about how much prophylactic oophorectomy reduces the risk of cancer in women with a BRCA1 or BRCA2 mutation. However, this preliminary information suggests prophylactic

oophorectomy can reduce the chance of developing ovarian cancer by as much as 90%. In addition, it appears that removing the ovaries before menopause also reduces breast cancer risk by as much as 50-60%. However, a prophylactic oophorectomy does not guarantee that ovarian and/or breast cancer will not develop.

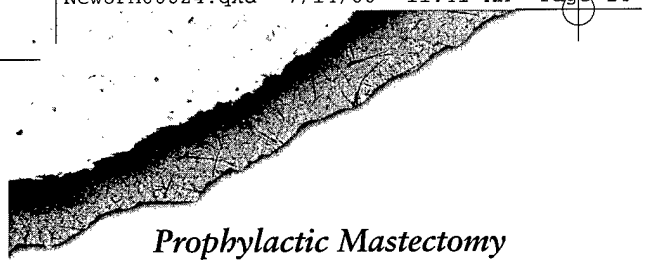
Some women may decide to have their uterus removed (hysterectomy) at the time they undergo prophylactic ooperectomy. Having a hysterectomy prevents development of endometrial cancer (cancer of the uterus) in the future. This issue may be particularly relevant to women who are considering tamoxifen for breast cancer risk reduction, as tamoxifen is known to increase the risk of endometrial cancer. However, having a hysterectomy at the time of oophorectomy requires a more extensive surgery, including the need for in-patient hospitalization and the small possibility of complications.

- What are the disadvantages of having a prophylactic oophorectomy?

Because the ovaries are totally removed, if a woman has not already experienced menopause, she will stop making estrogen and will undergo menopause, which may include some side effects. These may include hot flashes, mood changes, depression, fatigue/insomnia, and difficulty concentrating, among other symptoms. In most women these symptoms improve or disappear over a period of months. Removing ovaries in a post-menopausal woman will have no impact on menopausal symptoms because her ovaries have already stopped making estrogen. If a premenopausal woman has a prophylactic oophorectomy, she may choose to take hormone replacement therapy to ease the symptoms that occur after this surgery and to protect her heart and bones. In addition, because both ovaries are removed, pregnancy is not possible. Also, as with any surgical procedure, there is the risk associated with having surgery, which may lead to infections or other complications.




Laparascopic Surgery Post Oophorectomy



## *Prophylactic Mastectomy*

• What is a prophylactic mastectomy?

Prophylactic mastectomy is the removal of one or both breasts before there is any sign of breast cancer in order to decrease the chance of developing breast cancer. There are two types of prophylactic mastectomies: total and subcutaneous. A total mastectomy, also known as a simple mastectomy, removes the skin, nipple, and breast tissue. A subcutaneous mastectomy removes breast tissue, but leaves the overlying skin and nipple. A subcutaneous mastectomy leaves more breast tissue behind than a total mastectomy. Because leaving more breast tissue behind may be associated with a higher risk of developing breast cancer, many experts recommend total mastectomies for women with BRCA1 or BRCA2 mutations who choose to undergo prophylactic mastectomy.

• How is a prophylactic mastectomy performed?

A prophylactic mastectomy is an operation that requires a short stay in the hospital. Once preoperative tests are completed as an outpatient and the surgery is scheduled, a woman checks into the hospital. At the time of the surgery, she is put under general anesthesia. During this time, she is asleep and cannot feel pain while the surgeon removes both breasts. Reconstructive surgery can be done at this time. Once the surgery is completed, the woman remains in the hospital for several days to recover, with additional time if reconstructive surgery has been done. Bandages and drains must be maintained for several weeks until the area heals. Careful follow-up is needed to prevent any infection.

• What are the benefits of a prophylactic mastectomy?

Prophylactic mastectomy decreases the risk of developing breast cancer, although how much it decreases the risk in women with BRCA1 or BRCA2 mutations is unknown. The largest study with carefully collected information suggests a reduction of up to 90% in women with a strong family history of breast cancer. While this is a significant reduction, it does not guarantee that breast cancer will not develop.

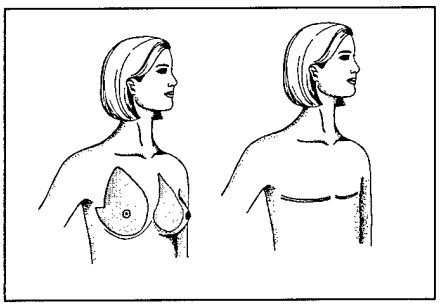
• Can breast reconstruction be done after prophylactic mastectomy?

Breast reconstruction is a surgical procedure that attempts to restore the shape of the breasts that have been removed. Reconstruction can be done at the time of the mastectomy or at a later date. When deciding about prophylactic mastectomy, it is important to recognize that reconstruction is not perfect, and may involve some complications.

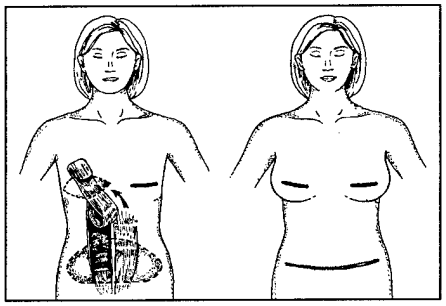
If a woman wishes to have reconstruction, there are several methods that can be used, although she may not be eligible for all of them. The first is a saline implant, which is placed under the muscle to replace the breast tissue that has been removed. Another option is to have a TRAM-flap, which involves moving of part of the abdominal (stomach) muscle and overlaying skin, and placing it on the chest in place of the breast tissue. Occasionally, a muscle from the back can be moved to replace the breast tissue. A plastic surgeon will evaluate each woman and suggest the possible reconstruction options and work with her to help her make a decision about reconstruction that is best for her.

• What are the disadvantages of a prophylactic mastectomy?

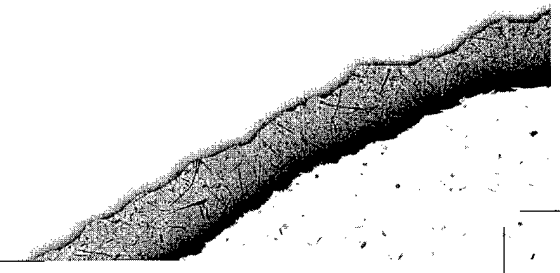
Aside from the cosmetic loss of the breasts, which can be partially corrected with reconstruction, the woman will lose sensation in the breast. This is because the nerves are cut around the breast during surgery. She will also lose the ability to breast feed due to the loss of the mammary glands, which produce milk.

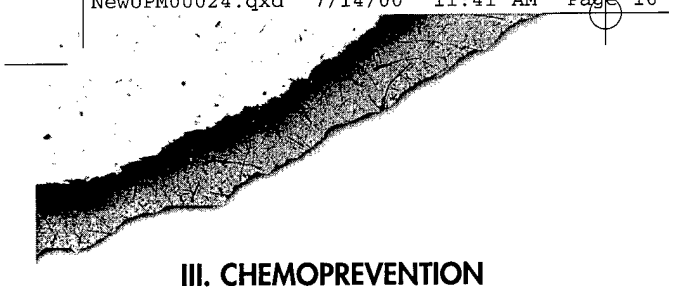


Simple Bilateral Mastectomy



TRAM-flap Reconstruction





## III. CHEMOPREVENTION

Chemoprevention, a new and growing field, involves taking a medicine to lower cancer risk. Currently, tamoxifen is the only medicine that has been approved by the Food and Drug Administration to reduce the risk of breast cancer. Oral contraceptives are not approved to reduce ovarian cancer risk, but several studies suggest they may be effective for this purpose.

### *Tamoxifen*

- What is it?

Tamoxifen, trade name Novaldex®, is a pill, taken once a day, which has been used to treat breast cancer for over 20 years. In the breast it acts as an "anti-estrogen" to block the action of estrogen. Recently, a large study showed that taking tamoxifen for five years lowers the occurrence of breast cancer in women who are at increased risk. Taking tamoxifen for longer than five years was not evaluated in this study, and the optimal length of time to take tamoxifen to reducing the risk of breast cancer has not been established.

- Who can take tamoxifen?

Women who have already had breast cancer often take tamoxifen to reduce the risk of recurrence. Now, women who are at increased risk of breast cancer because of a family history, age, or other risk factors are eligible to take tamoxifen to reduce the risk of first breast cancers. Although there has not been a specific study of tamoxifen in women with a BRCA1 or BRCA2 mutation, a woman with a BRCA1 or BRCA2 mutation is eligible because having this mutation is considered being at high risk.

- What are the benefits of taking tamoxifen?

One study suggests that tamoxifen reduces the risk of developing breast cancer by approximately 50%. Other studies have suggested that tamoxifen may also lower cholesterol levels and improve bone density. These effects may make women on tamoxifen less likely to have a heart attack and a bone fracture because of osteoporosis, the weakening of bones, although more studies need to be done.

• What are the disadvantages to taking tamoxifen?

Women who are over 50 are at the greatest risk of experiencing side effects from tamoxifen. Tamoxifen increases the rate of cancer of the uterus (endometrial cancer) slightly in women who have not had a hysterectomy. However, the risk is small, and this cancer is usually easily curable. Tamoxifen also increases the rate of blood clots, including clots in the lung (pulmonary embolism) and clots in major veins (deep vein thrombosis), and cataracts. Tamoxifen also may cause symptoms of menopause in women who have not yet undergone menopause, such as hot flashes, mood changes, insomnia, and vaginal dryness or discharge. However, tamoxifen does not cause menopause, and it is still possible to have children once the tamoxifen is stopped.

## *Oral Contraceptives*

• What are they?

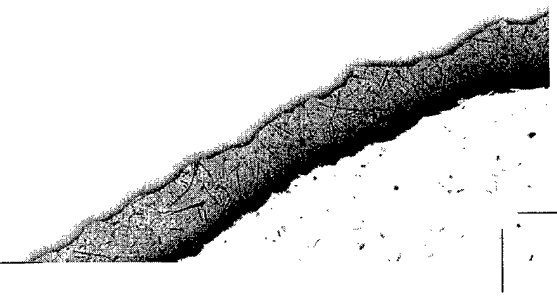
Oral contraceptives (birth control pills) are pills that are taken daily to prevent pregnancy. They generally contain low doses of estrogen and progesterone. These pills are also thought to lower the risk of ovarian cancer.

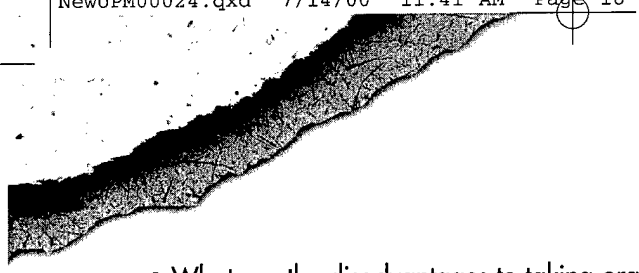
• Who can take oral contraceptives?

Women usually take oral contraceptives as birth control. Because of studies suggesting oral contraceptives reduce the risk of ovarian cancer, women who are at increased risk of ovarian cancer and have not yet experienced menopause may consider taking oral contraceptives to lower their ovarian cancer risk. Women with a BRCA1 or BRCA2 mutation may take oral contraceptives because of their increased risk of ovarian cancer.

• What are the benefits of taking oral contraceptives?

Several studies suggest that women who take oral contraceptives prior to menopause have about half the risk of developing ovarian cancer later in life as women who do not take oral contraceptives. In addition, oral contraceptives prevent pregnancy and may improve some premenstrual symptoms, such as acne, mood swings, and uterine cramping.





- What are the disadvantages to taking oral contraceptives?

Side effects of oral contraceptives include blood clots, including clots in the lung (pulmonary embolism), high blood pressure, stroke, nausea, headaches and weight gain in some women. Women who smoke cigarettes are at particular risk for developing blood clots and strokes. Some studies suggest early types of oral contraceptives may slightly increase the risk of breast cancer. However, new types of oral contraceptives have lower doses of estrogen and are unlikely to significantly increase breast cancer risk.

## IV. Hormone Replacement Therapy and Its Alternatives

At the time of menopause, a woman's ovaries stop producing estrogen and progesterone. Decreased levels of these hormones have many effects, including menopausal symptoms (such as hot flashes and mood swings), decreased bone density and increased cholesterol levels. After menopause, a woman's risk of osteoporosis and heart disease increases significantly. Several strategies have been proposed to help women manage the changes that occur with menopause, including use of hormone replacement therapy and other medications. Because these therapies have many effects that may compete with each other, deciding how best to manage the effects of menopause can be particularly difficult for women with BRCA1 or BRCA2 mutations.

### *Hormone Replacement Therapy*

- What is hormone replacement therapy?

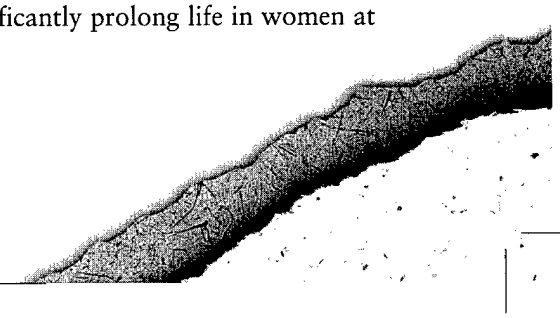
Hormone replacement therapy (HRT) contains estrogen or estrogen and progesterone, like a birth control pill. It is a pill that is taken once a day every day, or a patch that is worn on the skin like a Band-Aid. HRT is commonly used in women who have reached menopause to replace the female hormones that a woman's body no longer produces. All women on HRT receive estrogen, and women who have not had their uterus removed also receive progesterone. HRT is a consideration for women with BRCA1 or BRCA2 mutations if they choose to have a prophylactic oophorectomy before undergoing menopause, or when they experience menopause through natural aging.

- Who can take HRT?

Women who are undergoing or have completed natural menopause or women who have had their ovaries removed before they underwent natural menopause may consider taking HRT. If a woman has a personal history of breast cancer, most experts will not recommend HRT.

- What are the benefits of HRT?

HRT alleviates many of the symptoms of menopause such as hot flashes, sweats, mood changes, and disturbed sleep. HRT also decreases a woman's chance of developing coronary heart disease and osteoporosis by as much as 50%. HRT may also improve memory and reduce the risk of colon cancer. Overall, HRT has been shown to significantly prolong life in women at average risk of breast cancer.



Women may use HRT for their lifetime or for shorter periods of time following menopause. Many premenopausal woman who undergo prophylactic oophorectomy may choose to take HRT until about age 50 (the time of natural menopause) to alleviate the menopausal symptoms that develop because of the oophorectomy.

- What are the risks and disadvantages of taking HRT?

HRT, if taken after natural menopause, may slightly increase a woman's chance of developing breast cancer. The effect of HRT on the risk of breast cancer in women with BRCA1 or BRCA2 mutations is not currently known. Furthermore, the specific effects of HRT on breast cancer risk remain controversial.

Estrogen therapy without progestin may also increase the rate of cancer of the uterus. HRT may also increase the rate of blood clots. Less serious side effects include headaches, nausea, fluid retention, swollen breasts, weight gain, and vaginal discharge.

## *Raloxifene*

- What is it?

Raloxifene (trade name Evista®) is a drug that has been recently shown to prevent osteoporosis (the weakening of bones) in postmenopausal women. Raloxifene is a Selective Estrogen Receptor Modulator (SERM) that acts as estrogen on the heart and bones but like an anti-estrogen on the breast and uterus. Raloxifene is a pill that is taken daily.

- Who can take raloxifene?

Raloxifene is an alternative to HRT in post-menopausal women concerned about osteoporosis. It is especially attractive to women who are at an increased risk for breast cancer, as it does not increase breast cancer risk, and may actually decrease breast cancer risk.

- What are the benefits of taking raloxifene?

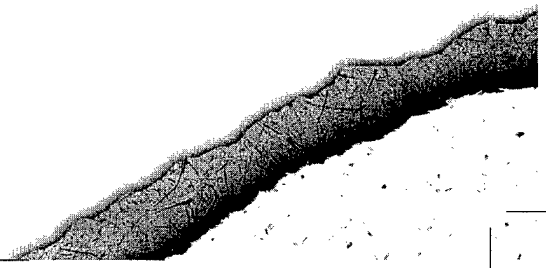
As a SERM, raloxifene has positive estrogen-like effects on bone density and cholesterol levels. It has been shown to prevent the development of osteoporosis and decrease LDL ("bad") cholesterol levels in post-menopausal women. These effects may result in a decrease of bone fractures and heart disease, although more studies need to be done. Because raloxifene blocks the action of estrogen on the breasts and uterus, it would be unlikely to increase

the risk for breast or endometrial cancers. In fact, preliminary data suggest that raloxifene does not increase uterine cancer risk and may decrease the incidence of breast cancer in post-menopausal women. Current studies are evaluating the effect of raloxifene on breast cancer risk.

It is important to recognize that raloxifene does not provide relief from menopausal symptoms such as hot flashes, mood swings, etc. that can be provided by HRT.

- What are the disadvantages of taking raloxifene?

Because raloxifene is a relatively new drug, we do not yet know all of its side effects. However, in the trials so far, raloxifene, like tamoxifen and HRT, has increased the rate of blood clots. Raloxifene may also cause hot flashes and leg cramps. Unlike tamoxifen, raloxifene does not appear to increase the risk of endometrial cancer.



## V. LIFESTYLE CHANGES

Some women who find out they have a mutation in BRCA1 or BRCA2 ask about lifestyle changes they can make to reduce their risk of cancer. Although there have been many studies of lifestyle and cancer risk, there are no specific indications that lifestyle changes can lower the risk of breast or ovarian cancer. Thus, it is difficult to make specific recommendations about lifestyle changes for women with BRCA1 or BRCA2 mutations. The following information is provided to help you understand what is known about the effects of lifestyle on the risk of breast and ovarian cancer.

- Alcohol

Several studies have found that women who have more than three drinks a day have an increased risk of breast cancer. A "drink" is considered a glass of wine, a bottle of beer or one shot of hard liquor. While no study has shown that cutting back on alcohol intake can lower a woman's risk of breast cancer, it is reasonable to keep alcohol intake to less than three drinks a day.

- Diet

The effect of dietary fat on the risk of breast cancer has been studied many times with mixed results. Some studies have found that high fat diets increase the risk of breast cancer, while others have found no association. Again, while no study has shown that decreasing dietary fat can lower a woman's risk of breast cancer, it is reasonable to keep dietary fat below the recommended 30% of total caloric intake.

Vitamins and dietary supplements have received a lot of attention as possible cancer risk reduction treatments. Because there are no trials that support the benefit of supplements in reducing cancer risk, specific supplements are not recommended at this time. While the decision about taking any of these supplements is highly individual, it is important to remember that the risks of many of these supplements are not yet known either. Many claims about protecting against cancer are exaggerated or not true. Some supplements may even be harmful.

*Dietary supplements that have been publicized as preventing cancer include the following supplements:*

***Antioxidants*** are thought to combine with free radicals, which may cause cancer by damaging the DNA in cells, to reduce their ability to do damage. Vitamins A, C, and E, which are found in fruits and vegetables, are antioxidants.

***Selenium*** is a nutrient found in food that has been shown in a few studies to be associated with a lowered incidence of breast cancer.

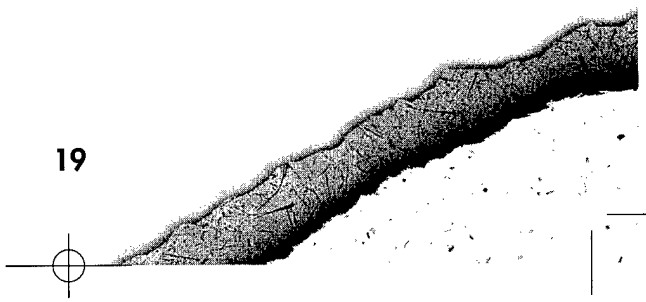
***Genistein***, which is found in soy products such as tofu, is a phytoestrogen, or weak plant estrogen. This compound may block the action of stronger estrogens in the breast, possibly lowering the risk of developing breast cancer.

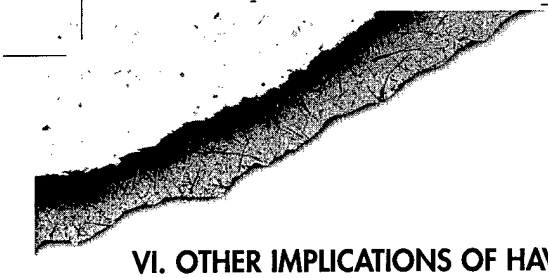
Countless other foods, ranging from flaxseed to mushroom tea, have been proposed as having cancer fighting properties. While many important medicines have come from plant sources, none of these foods have yet been proven to reduce cancer risk. Importantly, by eating a well-balanced and healthy diet, most of the natural cancer fighting agents are automatically included. The National Cancer Institute recommends eating at least five fruits and vegetables every day to reduce the risk of developing cancer.

- Exercise

Several studies have found that women who perform aerobic exercise for at least four hours a week have a lower risk of breast cancer than women who do not exercise. While no study has shown that becoming more active will specifically reduce the risk of developing breast cancer, in general, exercise has been shown to be beneficial to health and may also decrease the risk of breast cancer.

In the end, it is important to have a healthy diet and exercise, regardless of a woman's risk for breast and ovarian cancer. The American Cancer Society has issued guidelines promoting a balanced diet that is low in fat, high in fiber, and includes plenty of fruits and vegetables. These recommendations can be found on-line at www.cancer.org, under the subheading prevention, or from your physician. These are useful to any woman interested in improving her health, regardless of risk for breast and ovarian cancer.





## VI. OTHER IMPLICATIONS OF HAVING A BRCA MUTATION

• Implications for family

If a woman or man tests positive for either a BRCA1 or BRCA2 mutation, his/her children have a 50% chance of also having the BRCA1 or BRCA 2 mutation, regardless of whether they are male or female. Other first-degree relatives such as brothers and sisters also have a 50% chance of carrying the mutation. Less closely related blood relatives may have lower chances of carrying a mutated BRCA1 or BRCA2 gene.

Genetic testing is a personal decision, but learning about the presence of an inherited mutation that increases risk for cancer can also affect other family members, and possibly even family relationships. Other relatives could learn about their cancer risk through testing a parent, brother, sister or cousin, for example, and this information may or may not be welcome. Once a mutation has previously been identified in a family, testing other family members is technically simpler, less expensive, and highly informative. While we strongly encourage people to share genetic testing information with relatives, ultimately each family member should choose for him or herself whether or not to be tested.

• Implications for Health Insurance

Some individuals who learn they have a BRCA1 or BRCA2 mutation are concerned about the possibility of genetic discrimination in health or life insurance. Although many activists, including representatives from the University of Pennsylvania, are working with groups to support protection from the possibility of genetic discrimination, discrimination has never been associated with genetic testing for BRCA1 or BRCA2 mutations. Furthermore, individuals who have been diagnosed with cancer in the past are not thought to be at any increased risk of discrimination based on genetic testing.

Most Americans get their medical insurance through their employer, and as part of a group. Even people who have their own businesses often join with a group to buy into a medical insurance plan. People who have health insurance through a group are insured with others at the same rate. A group health plan can offer any type of available insurance, such as Blue Cross/ Blue Shield, HMO insurance, or contract with any plan it chooses. A federal law enacted

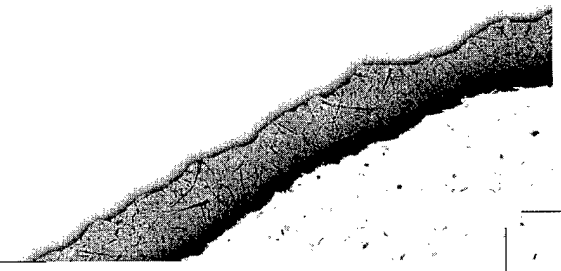
in 1997 (the Health Insurance Portability and Accountability Act, or HIPAA) makes it illegal to single someone out in a group health plan for higher or lower payments for their medical insurance. The same federal law makes it illegal to drop a person, exclude someone, or deny any medical treatment, including for cancer, by saying the person has a pre-existing condition.

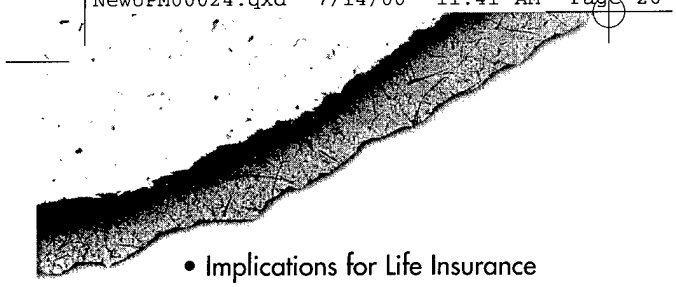
The HIPAA law applies as long as a person maintains continuous group health insurance coverage with the same, or with a new group health insurance plan. Therefore, people who change jobs do not need to fear being denied access to the new group health plan policy. The policy can be through an employer, or any group, such as a trade group, or retired persons group such as AARP.

People who have group insurance are usually not underwritten. Underwriting is the process in which an insurance company tries to determine what a person may actually cost to insure. People are underwritten for car insurance when they are asked how many accidents they have had, their age, their gender, and where they live. Each of these things can affect their insurance rates. Underwriting for health insurance may include questions about weight, smoking, and the presence of significant medical conditions like heart disease or cancer. If a person signed up for medical insurance without filling out a detailed medical questionnaire, then he/she was not underwritten.
And, if he/she was not underwritten, then past medical history, including risk of cancer or genetic testing, will not be considered when setting the rate he/she pays for medical insurance. People with government-sponsored insurance, such as Medicare and Medicaid, or most group insurance are not underwritten.

A small number of Americans purchase their own individual health insurance, outside a group and are underwritten. They are not protected through the same federal law that protects those in group health plans. However, there are many states that have individually enacted laws to prevent genetic discrimination, whether a person is in a group or private plan (in 1999, New Jersey had a comprehensive protection law, and Delaware and Pennsylvania had no laws). There are also limits to state laws that will vary depending on the state and legislation. There are only a handful of documented cases of genetic discrimination in this country, none of which were associated with cancer, thus, people assume their personal risks are much higher than they are.







- Implications for Life Insurance

Individuals who purchase life insurance through their employers and are not underwritten are unlikely to experience changes in life insurance coveage because of genetic testing. For people who are underwritten for life insurance, a personal or family history of cancer, with or without genetic testing, could affect life insurance rates. Although most life insurance companies do not ask about genetic testing, this may change in the future. Some people choose to purchase life insurance before undergoing genetic testing. Legislative and policy efforts are currently trying to decide whether life insurance companies should have access to genetic test results.

- Implications for Employment

Employment discrimination occurs if an employer singles people out with any medical condition that may affect how much an employee could cost a company. For example, an employer may believe that a person with a prior history of cancer is at risk of being absent more, and choose to promote someone else over this person, even if they are similarly qualified. For this reason, we suggest not discussing medical information, including information about genetic testing, in the workplace. It is hard to know how common employment discrimination is, since it is rarely reported.

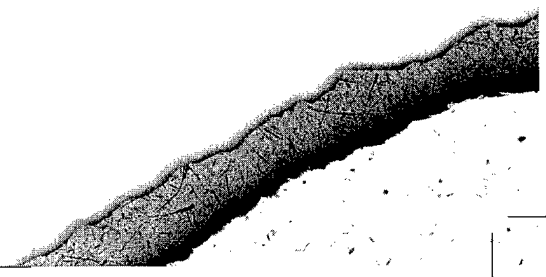
- Implications of Sharing Results

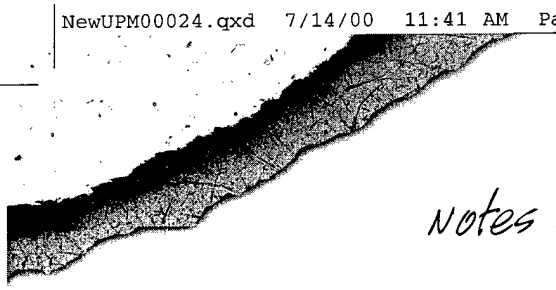
There are two ways of being tested and receiving results; through clinical testing and through research testing. Clinical testing is a process that involves your results being placed in your medical records, which are accessible to doctors and health insurance companies.

Research results from genetic testing are considered confidential, and do not have to be placed in a medical record. Some people who underwent research testing wonder whether or not they should share this information with their doctors and other health care providers, since then the information will likely be placed in a medical chart. This is a personal decision, and the choice may be affected by the personal situation, as previously described.

There may be substantial benefits to sharing information about the presence of a gene mutation with doctors, since they are partners in delivering the most appropriate, personalized health care to their patients. A woman may be facing some difficult decisions, such as whether or not to take hormone replacement therapy, or have prophylactic surgery, that she might want to discuss with her personal doctors. In addition, as the field of cancer genetics advances, doctors may be able to alert their patients to new interventions that may be tailored to those with genetic risk.

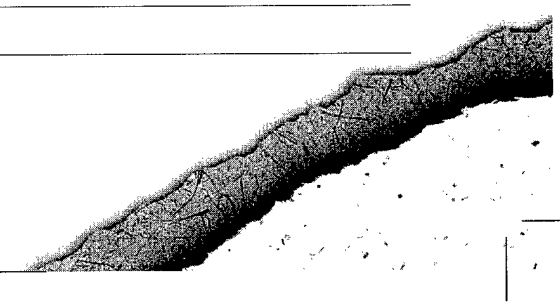
In addition, women often choose to inform their insurance companies to get coverage for genetic testing, preventive surgery, or other management options, since paying out of pocket can become a considerable expense.

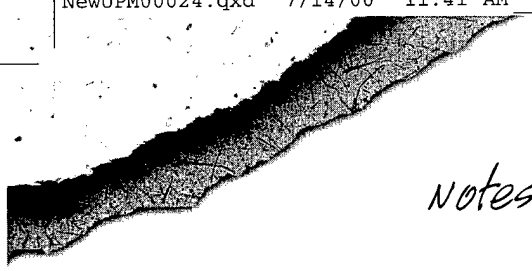




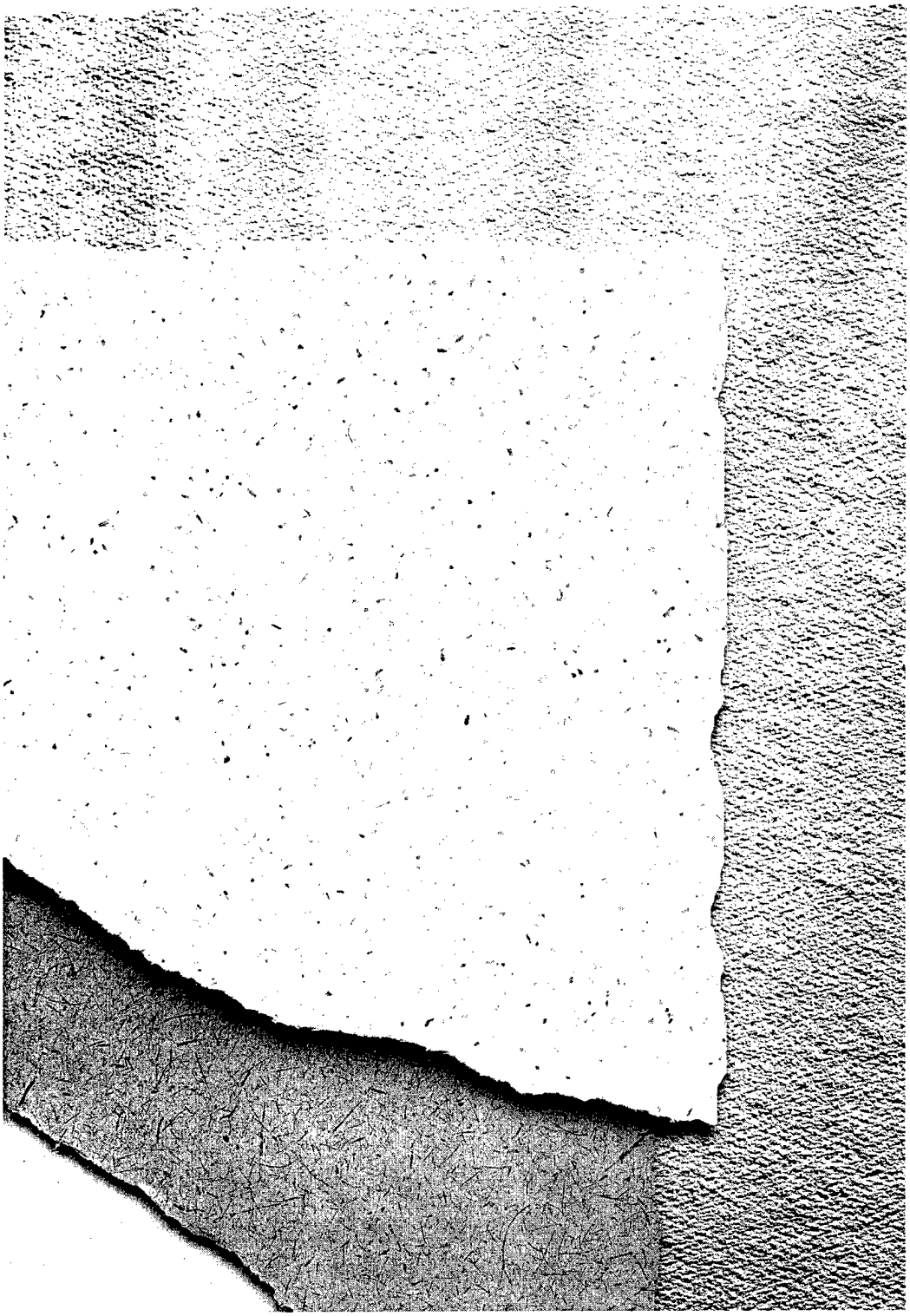
# Notes & Numbers

# Notes & Numbers





# Notes & Numbers



# Appendix B:
# Computer Decision Support System Protocol

# DOD Decision Support System

## Instructions for use

**To install:**

- You must have DATA 3.5 and Excel97 installed on your computer
- Create a folder on the D: drive of your system: D:\USERS\DOD\MODELS
- Copy all the files on this diskette to this folder. These include the current model and the Excel graphing application.
- Make sure the table (.tbl) files are in the appropriate DATA subfolder

**Overview of the procedure:**

- Open DATA and select the appropriate .tre file (Fig. 1)
- Set the parameters appropriate for a given subject (Fig 2.)
- Run the model (Figs. 3-4)
- Graph the output in DATA, saving the graph data to a text file (Figs 4-13)
- Open the Excel graphing application included on the distribution diskette, and run it accordoing to the instructions given below in Figs. 14-17

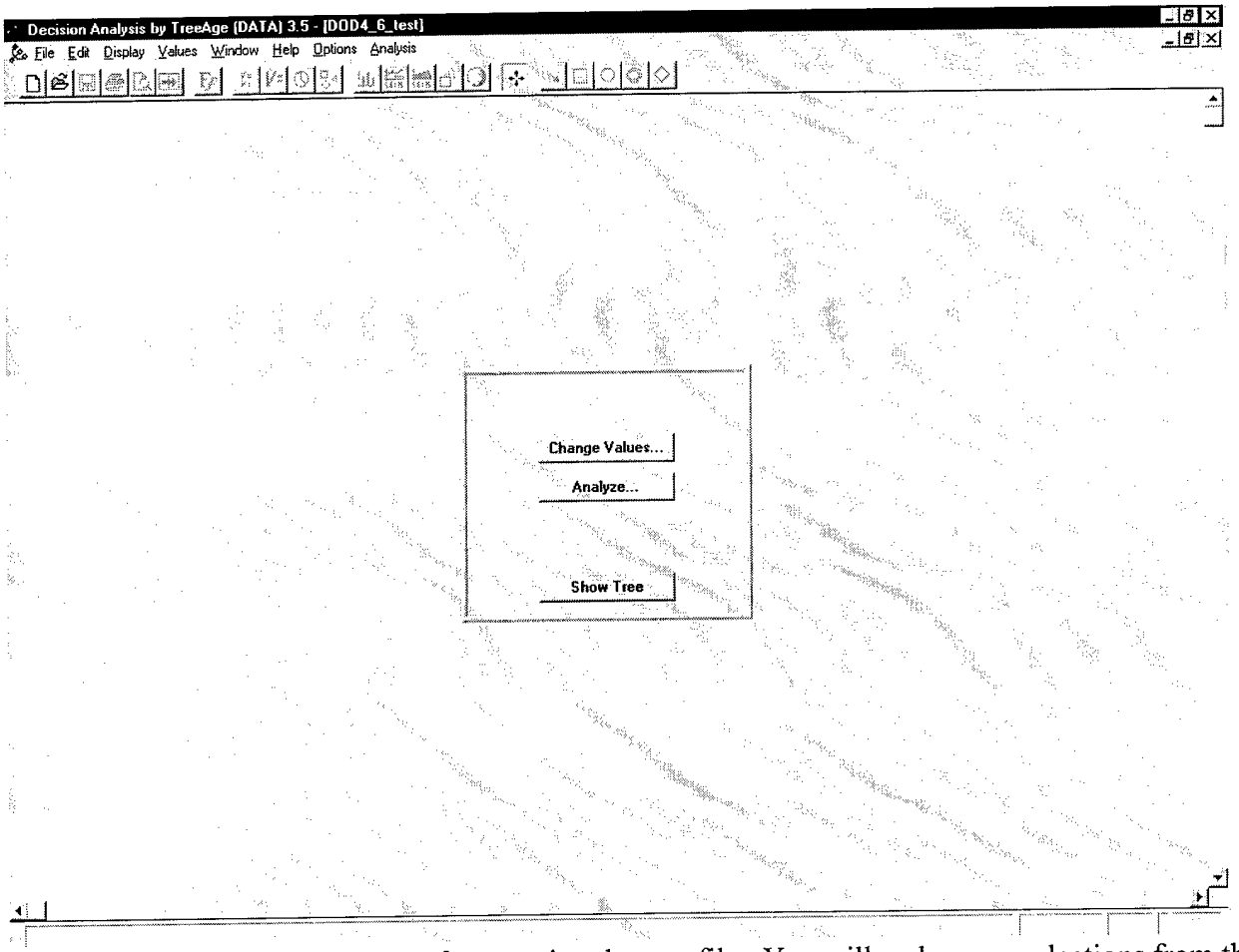



Fig 1. Appearance of DATA after opening the tree file. You will make your selections from the buttons, selecting first Change Values and then Analyze.

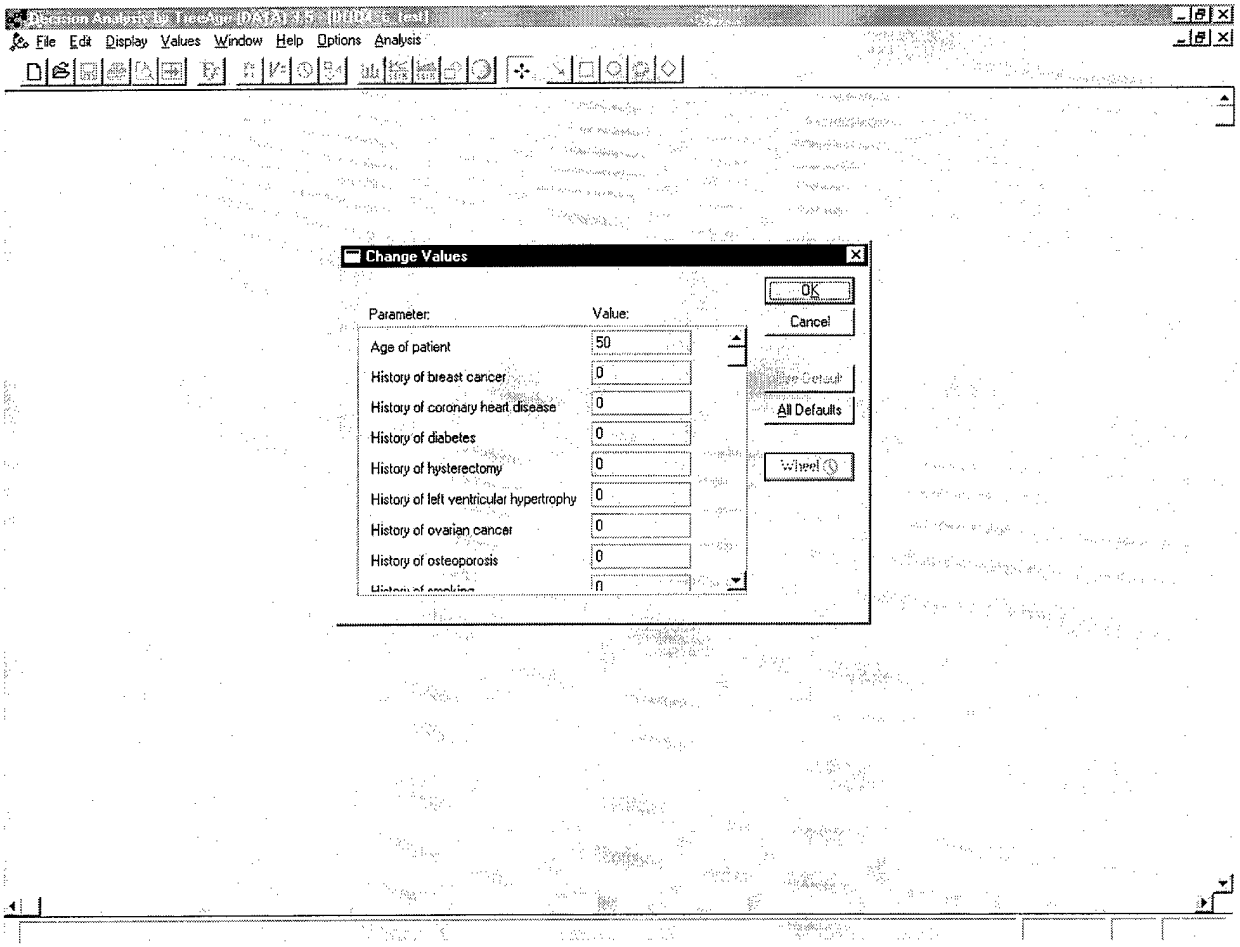



Fig 2. After selecting Change Values, you'll see this window, in which you change the subject's parameters as prompted. If you exceed the allowed range for any item, you'll see a warning box alerting you to the proper range. Be sure to consult the list of allowed treatment combinations:

PM alone
PM+Raloxifene
PM+Hormone replacement therapy
PM+Oral contraceptives
PM+Prophylactic oophorectomy+Hormone replacement therapy
PM+Prophylactic oophorectomy+Raloxifene

Tamoxifen alone
Tamoxifen+Prophylactic oophorectony

Prophylactic oophorectomy alone
Prophylactic oophorectomy+PM
Prophylactic oophorectomy+Hormone replacement therapy
Prophylactic oophorectomy+Tamoxifen
Prophylactic oophorectomy+Raloxifene

Hormone replacement theraphy alone

Raloxifene alone

Oral contraceptives alone

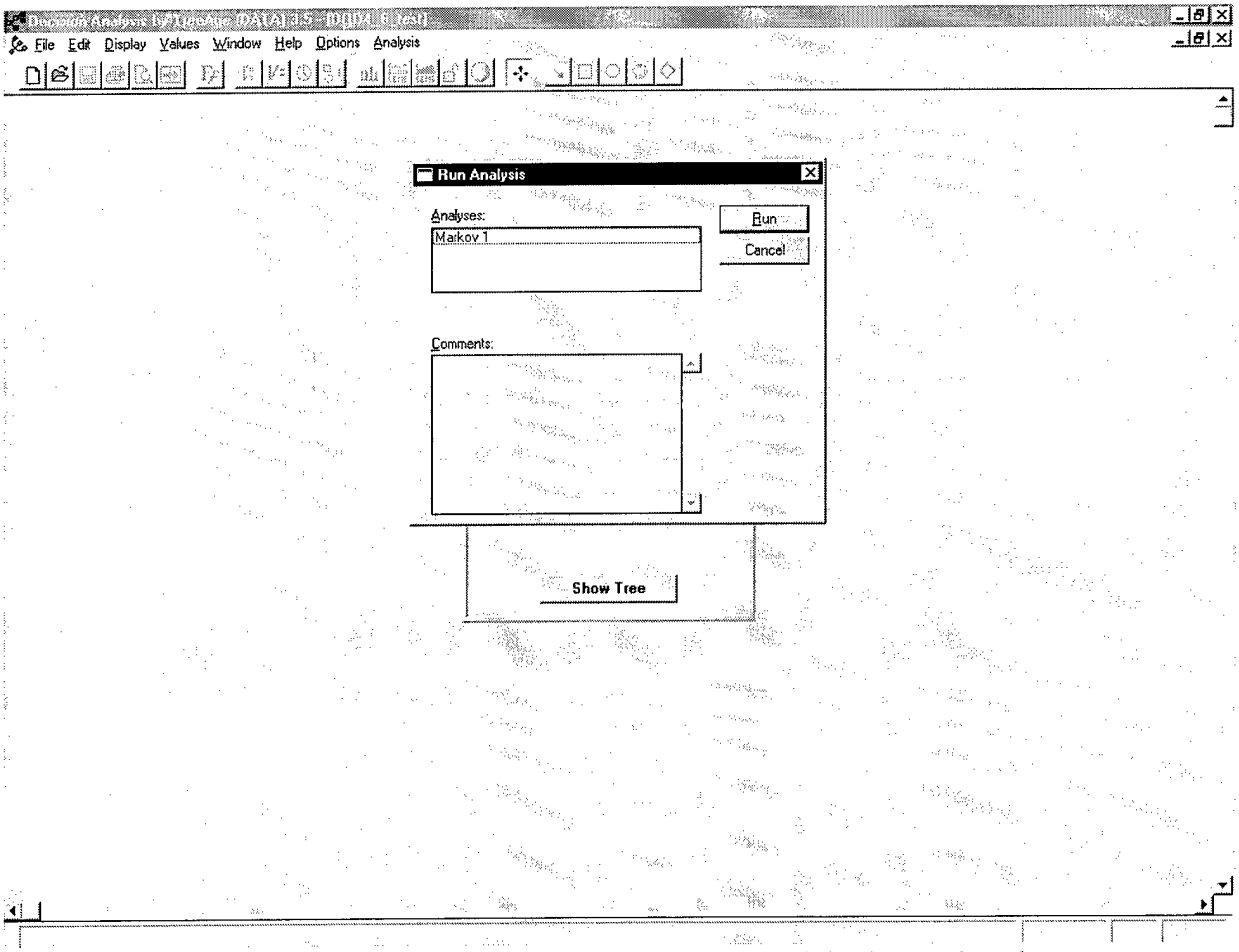



Fig 3. After changing the parameter values for the subject, click in the Analyze button to start the analysis. Only the Markov analysis is present in this application, so select that and click on the Run button.

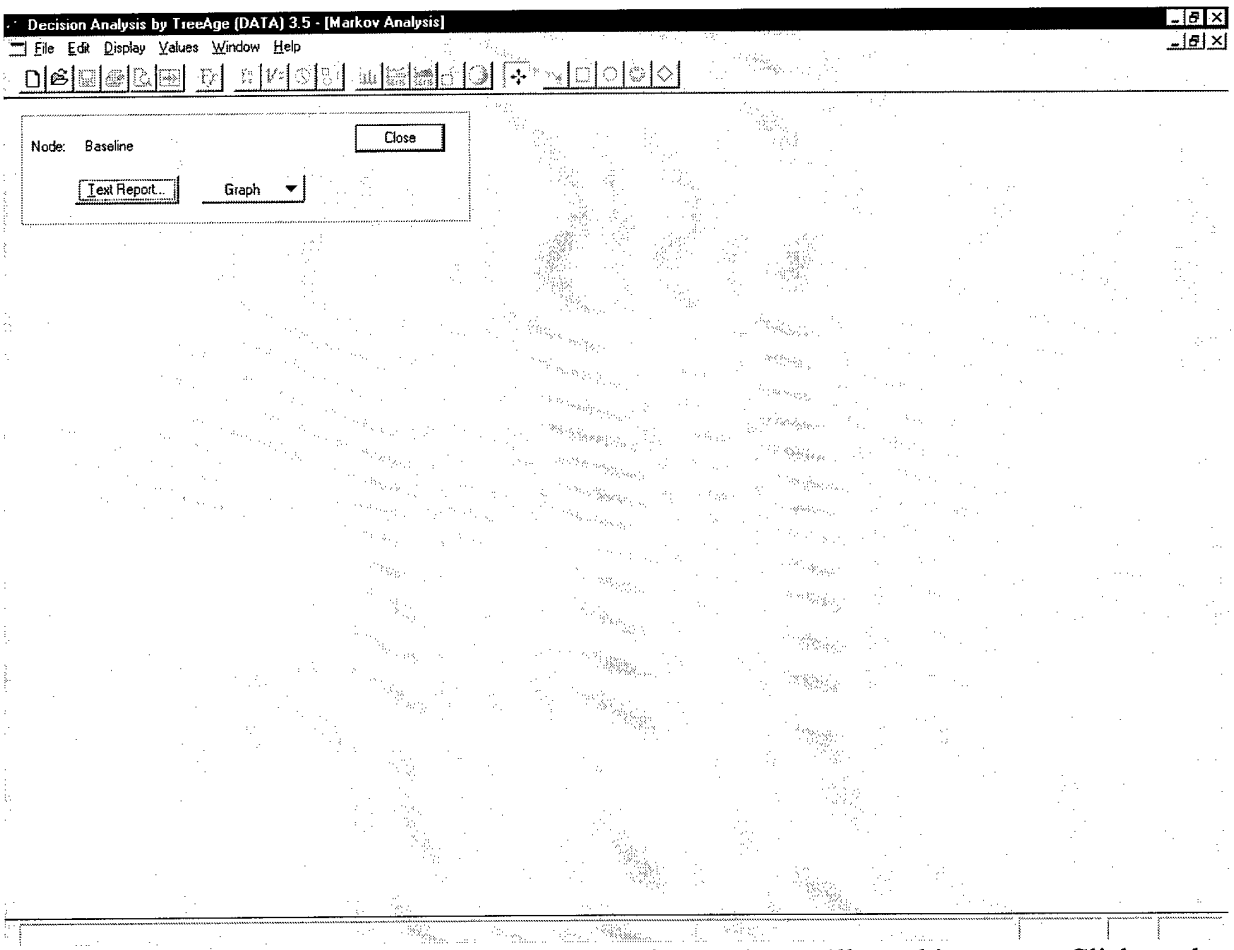



Fig. 4. The analysis takes a few seconds to run. Afterwards, you'll see this screen. Click on the Graph button to obtain the Graph Type menu that you'll see in Fig. 5.

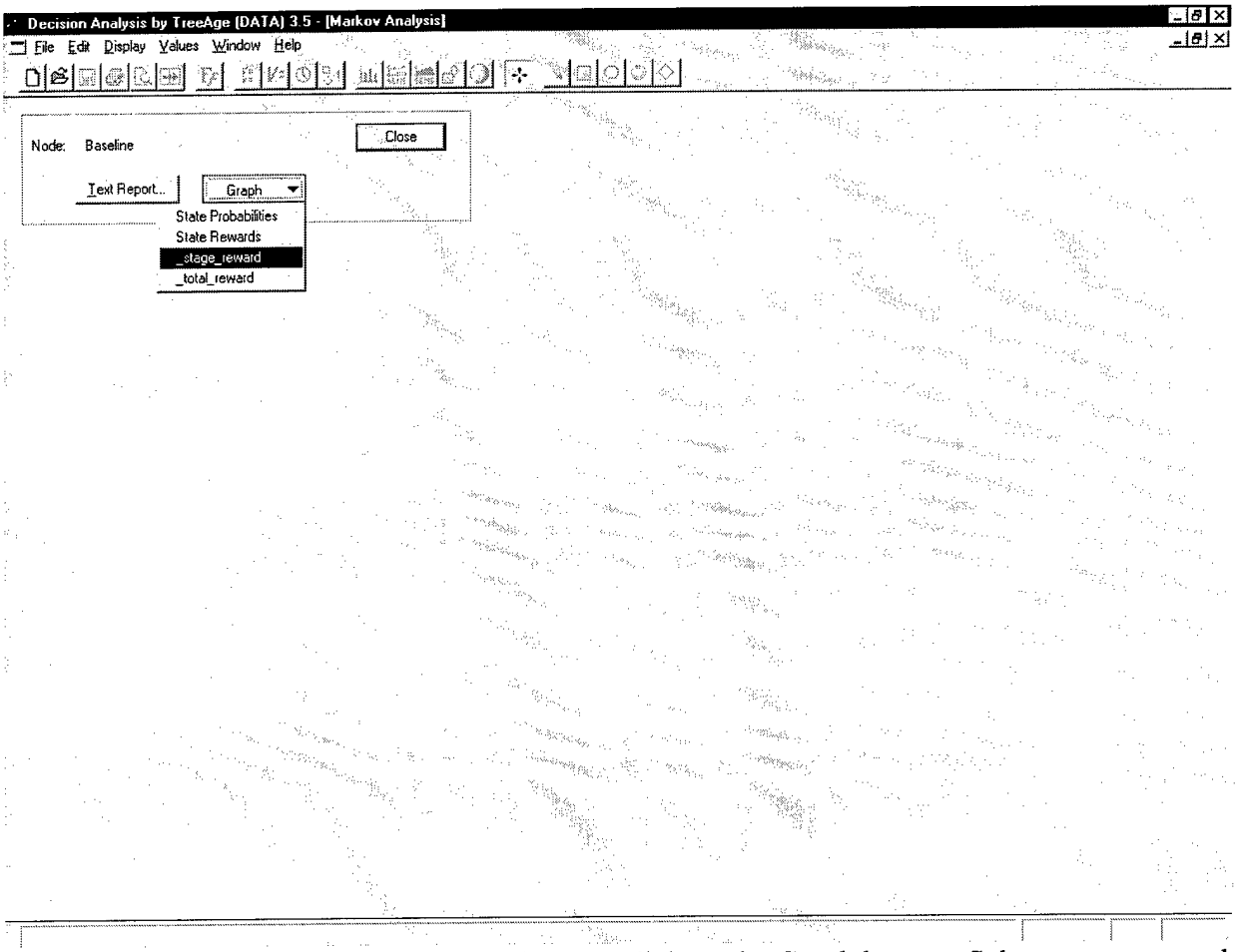



Fig. 5. The Graph Type menu appears after you click on the Graph button. Select _stage reward by clicking on this option.

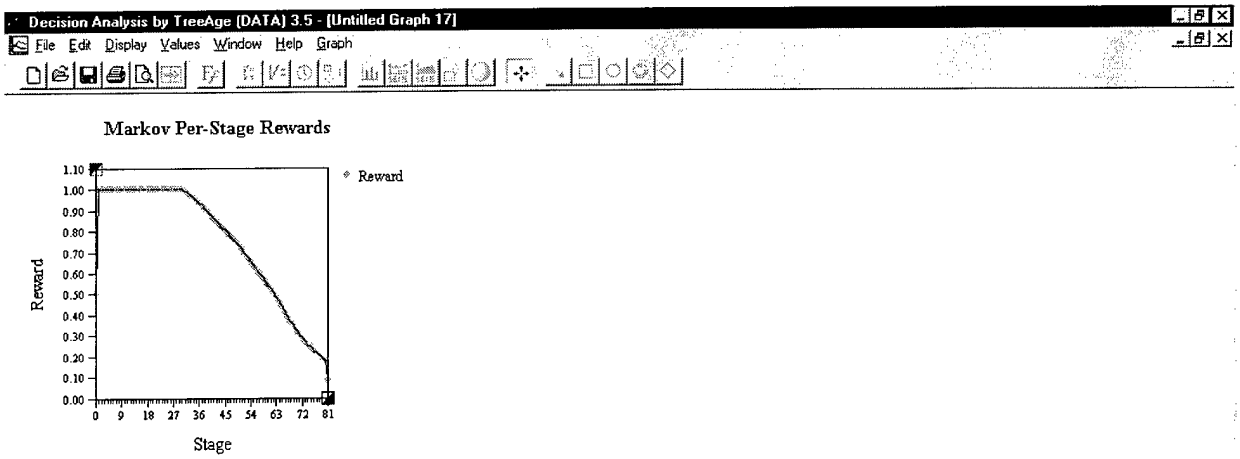



Fig 6. This is a stage reward graph, but it is not the one you'll be printing. Think of this graph as a kind of preview of the final product, which will be prepared and printed later.

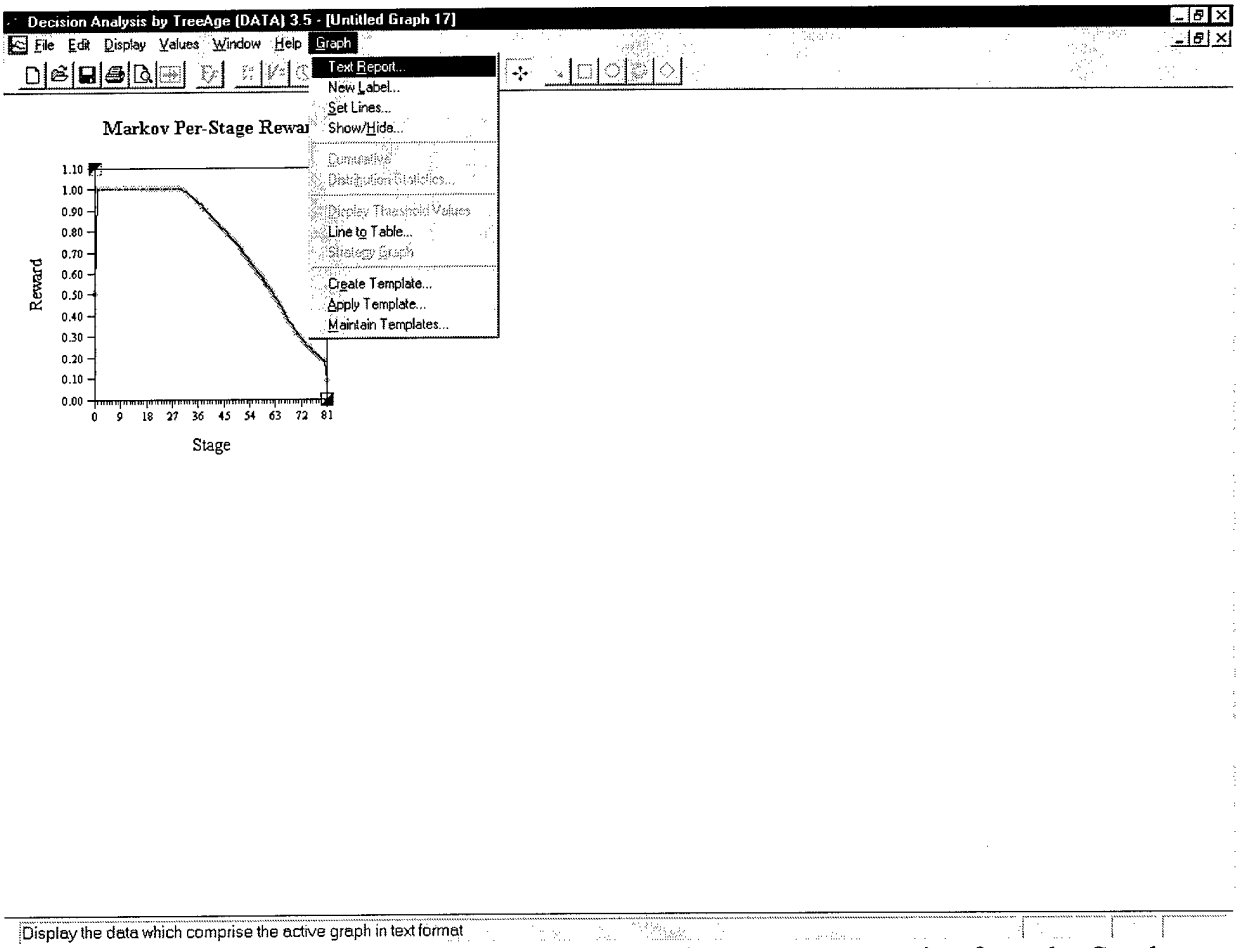



Fig. 7. After the graph in Fig. 6 has appeared, select the Text Report option form the Graph menu on the menu bar. You will be writing the data that created this graph to a file for import into Excel so that a graph of better quality can be created.

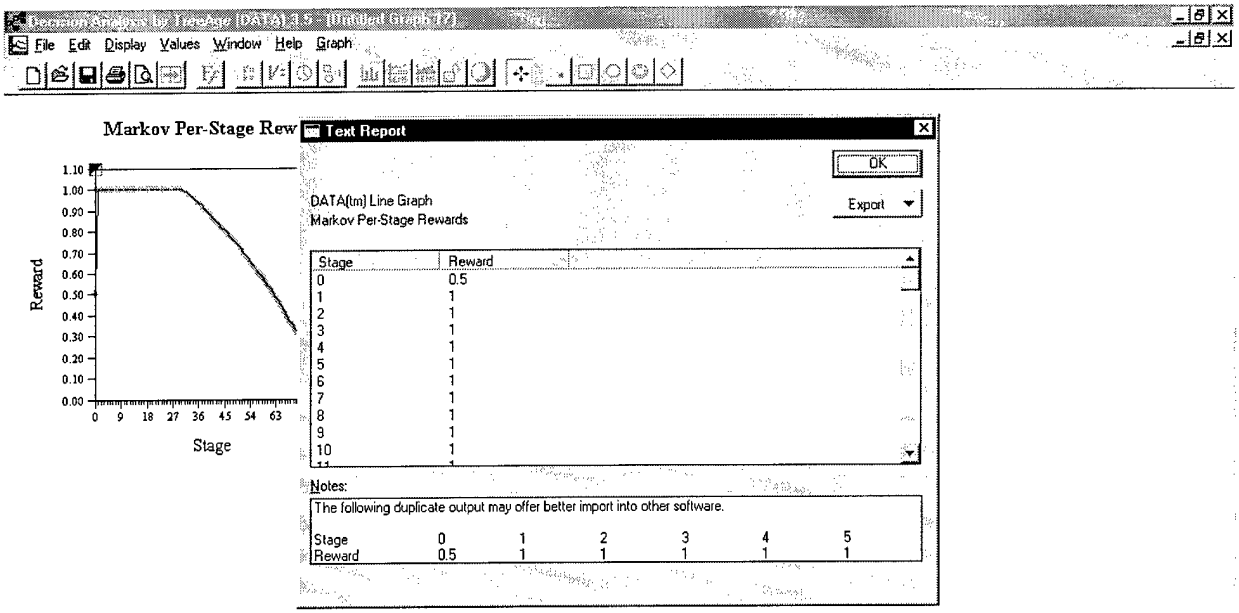



Fig. 8. The Text Report window appears after selecting this option form the Graph menu. This is a preview of the contents of the text file you'll be creating. At this point, click on the Export button, to create the file.

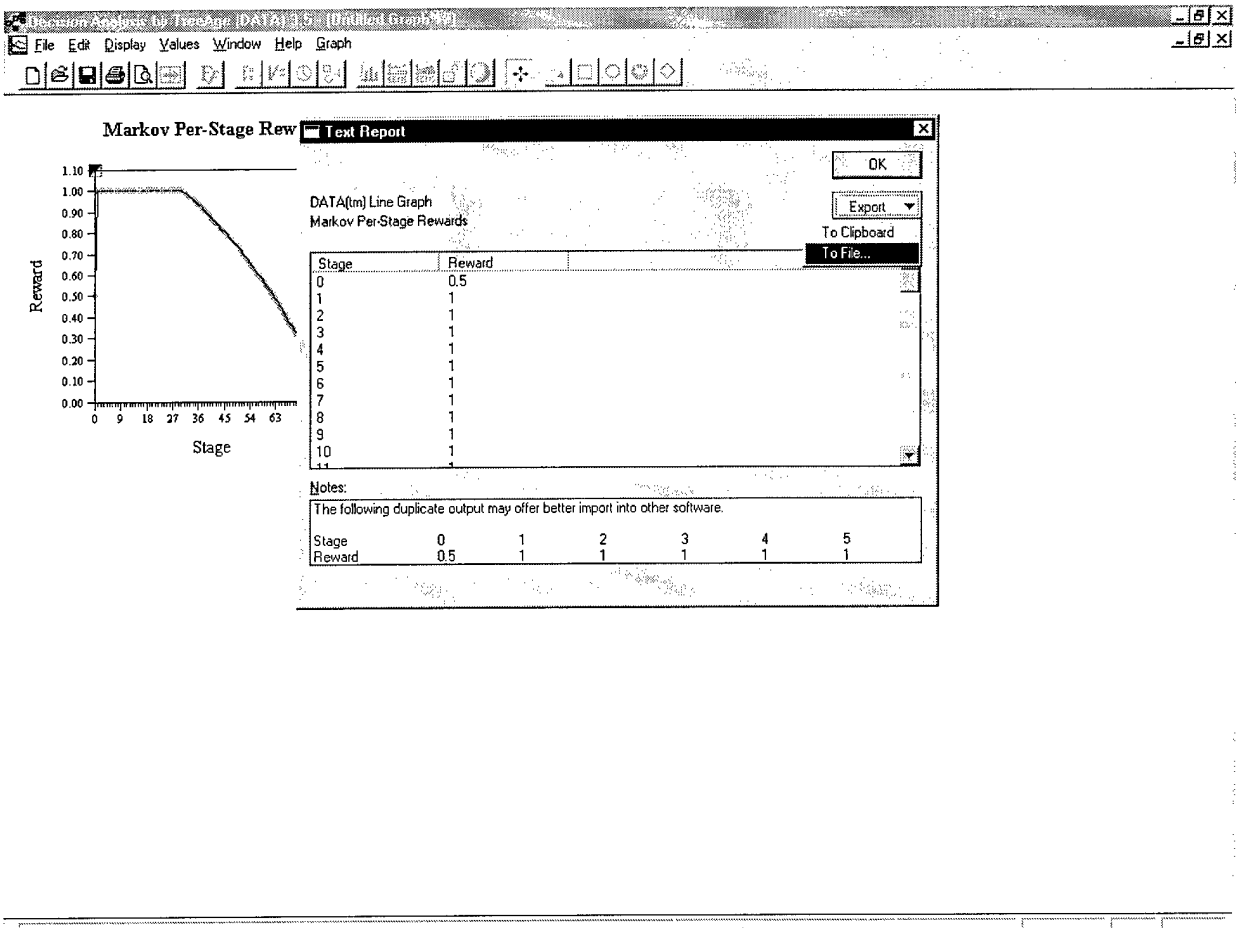



Fig. 9. When you click on the Export button, you have two options: save the file to the clipboard or to a file. Select the To File option.

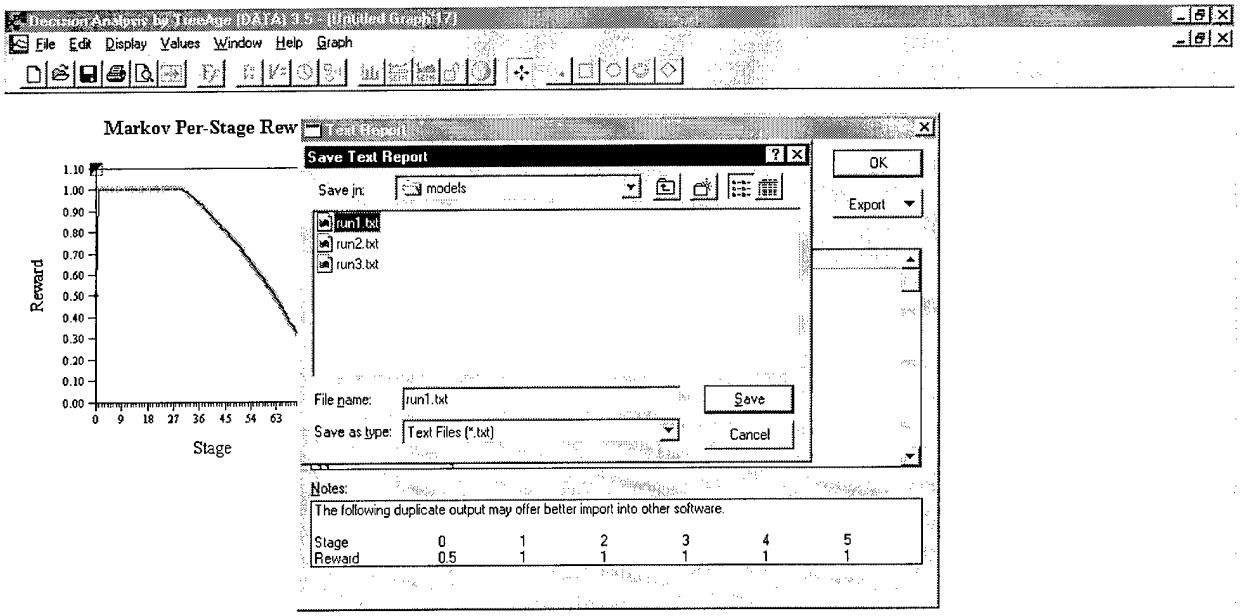



Fig. 10. When you select the To File option, you'll be presented with a typical save-file dialog. *Make certain that the location is specified as d:\users\dod\models and the file name is run1.txt.*

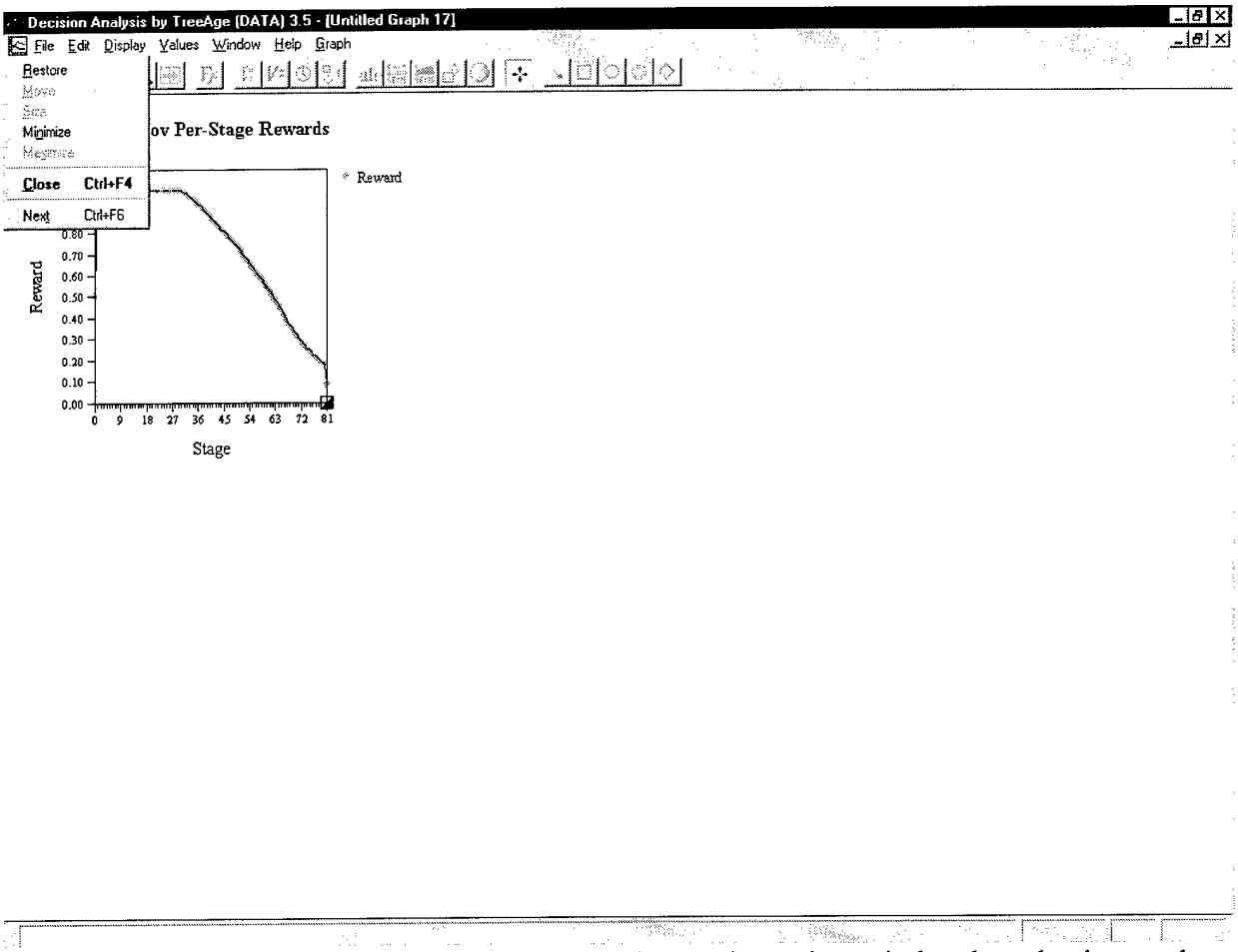



Fig. 11. After you have saved the text file, close the graph preview window by selecting on the Close option of the File menu.

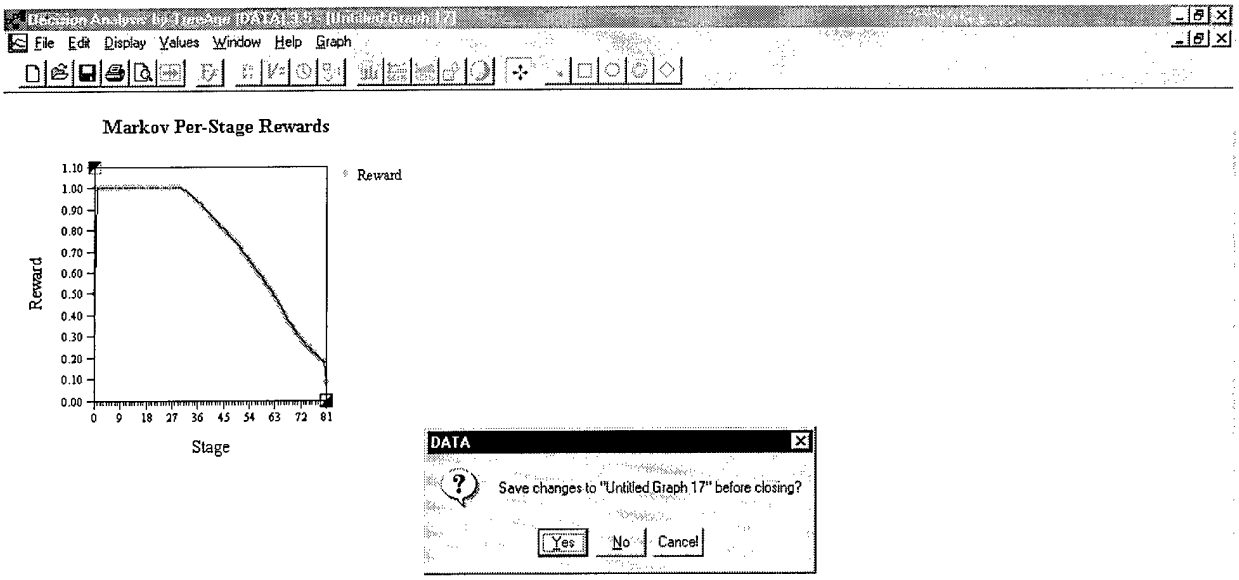



Fig. 12. You will be prompted to save the graph before you exit this screen. There is no need to do so, as you will not be using this graph, so click on the No button.

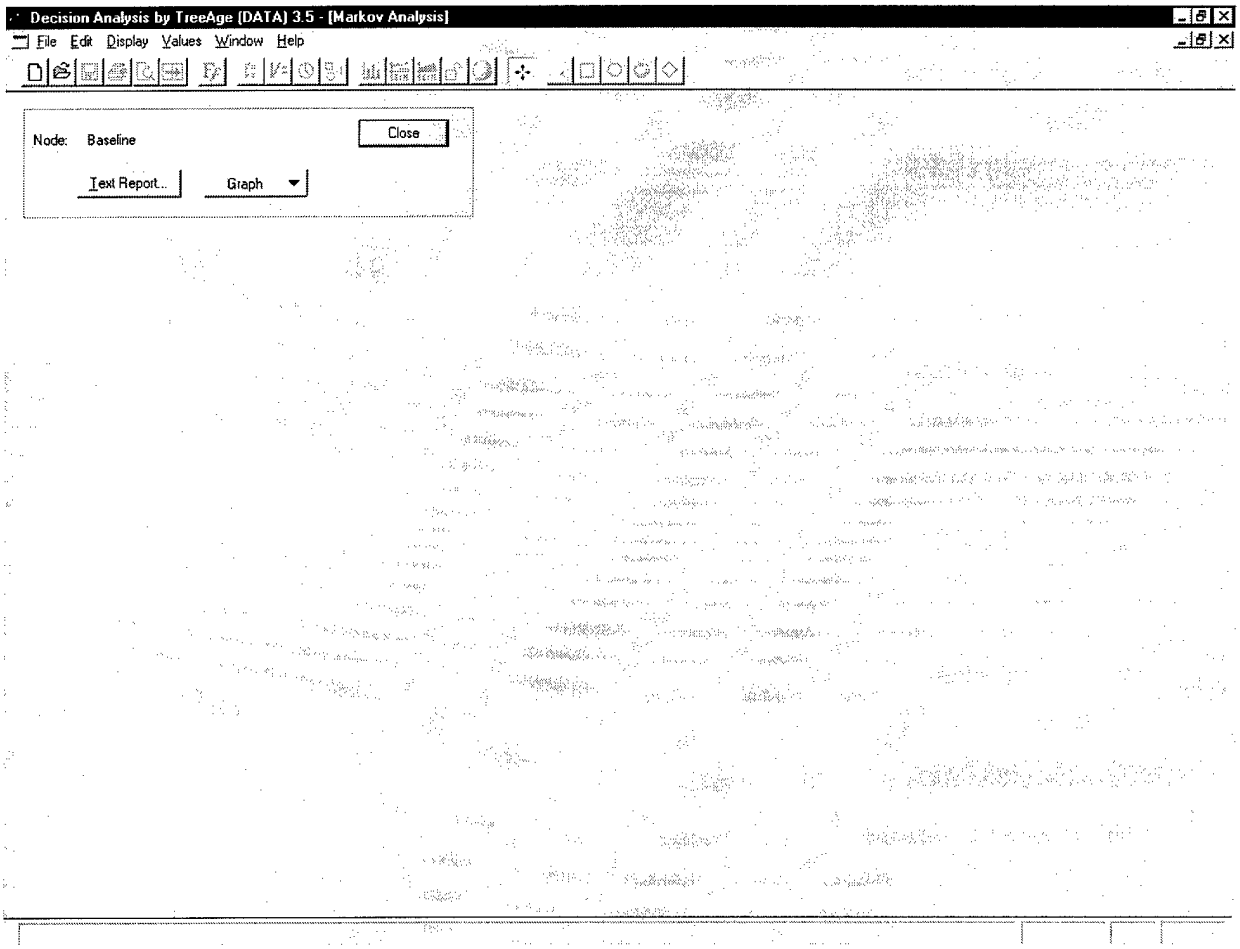



Fig. 13. You will then be returned to the opening graph preview window. Click on the Close button to exit this window and return to the opening screen of the DATA application. At this point, you can go on to edit the parameters for a subject and create new graphs for these, or you can proceed to the graphing application, which is shown in Fig. 14.

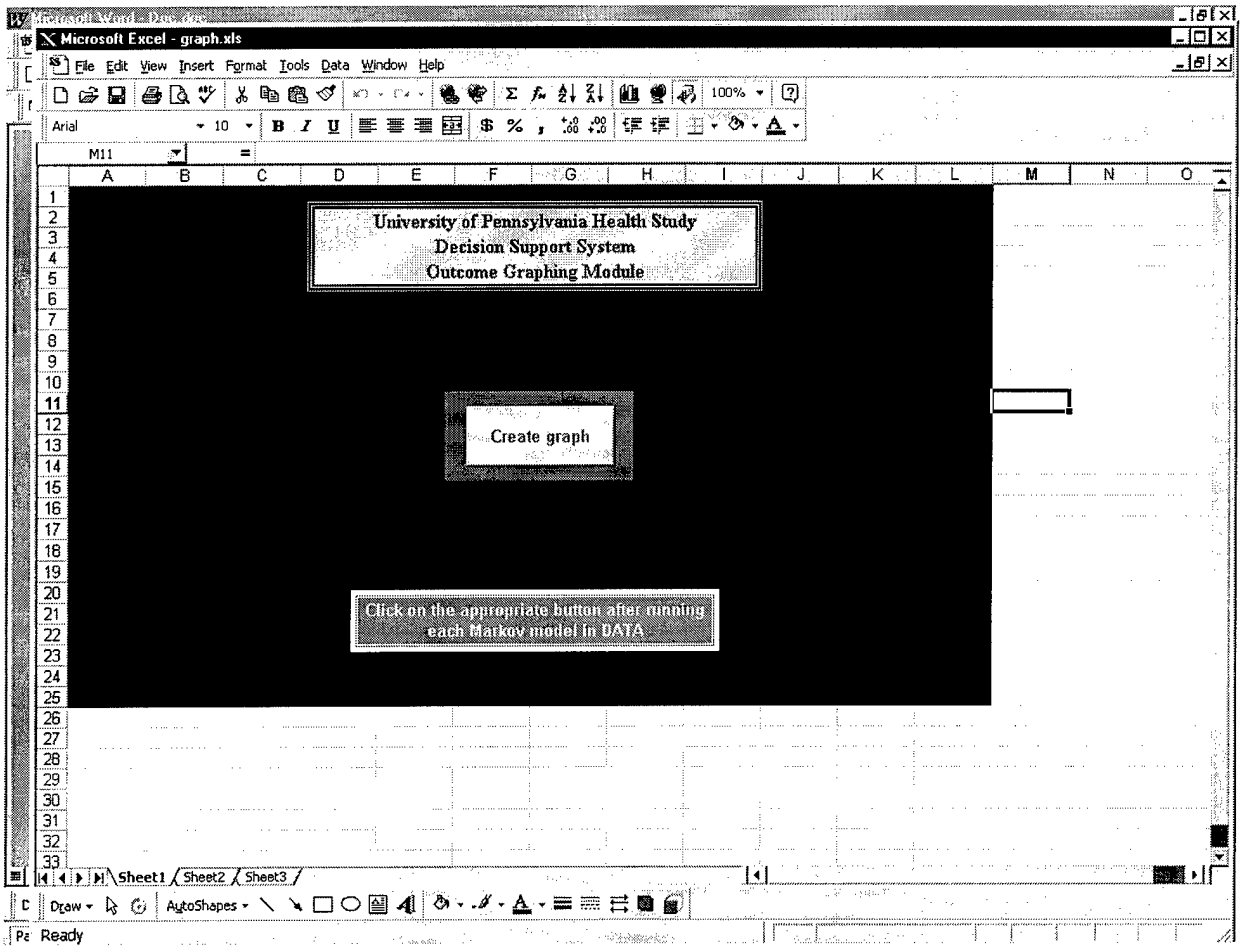



Fig 14. The opening screen of the graphing application. It is started by opening Excel and selecting the spreadsheet file GRAPH.XLS. Like the DATA application, this is in the d:\users\dod\models folder. You will see other spreadsheets in this folder as well. Do NOT open these. Make certain you open only GRAPH.XLS. To obtain a graph of the subject's data, simply slick on the button labeled "Create Graph."

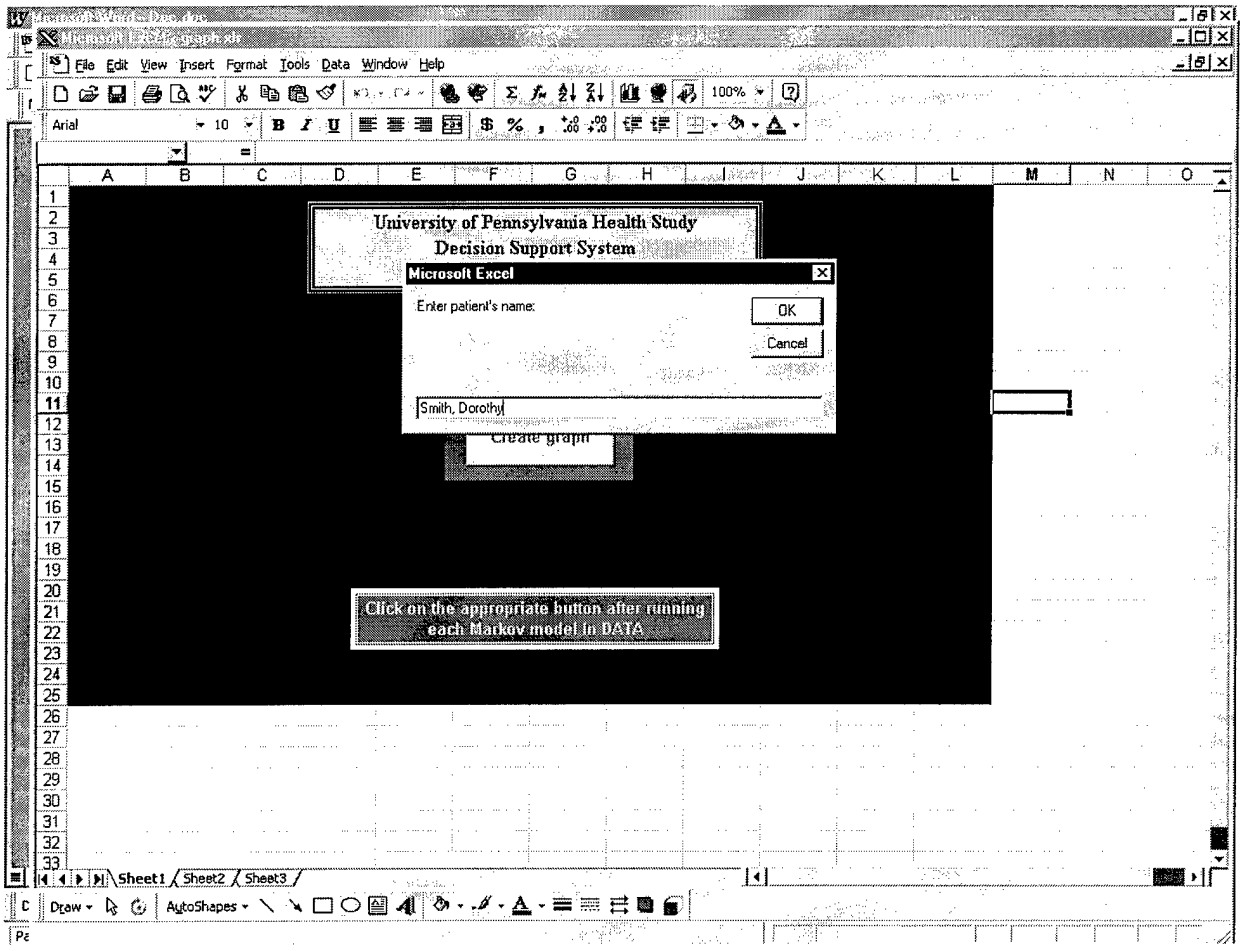



Fig. 15. After clicking on the Create Graph button in Fig. 14, you will be prompted to enter the patient's name. Enter this as: last name, first name, as shown in the figure above, and then click on the OK button.

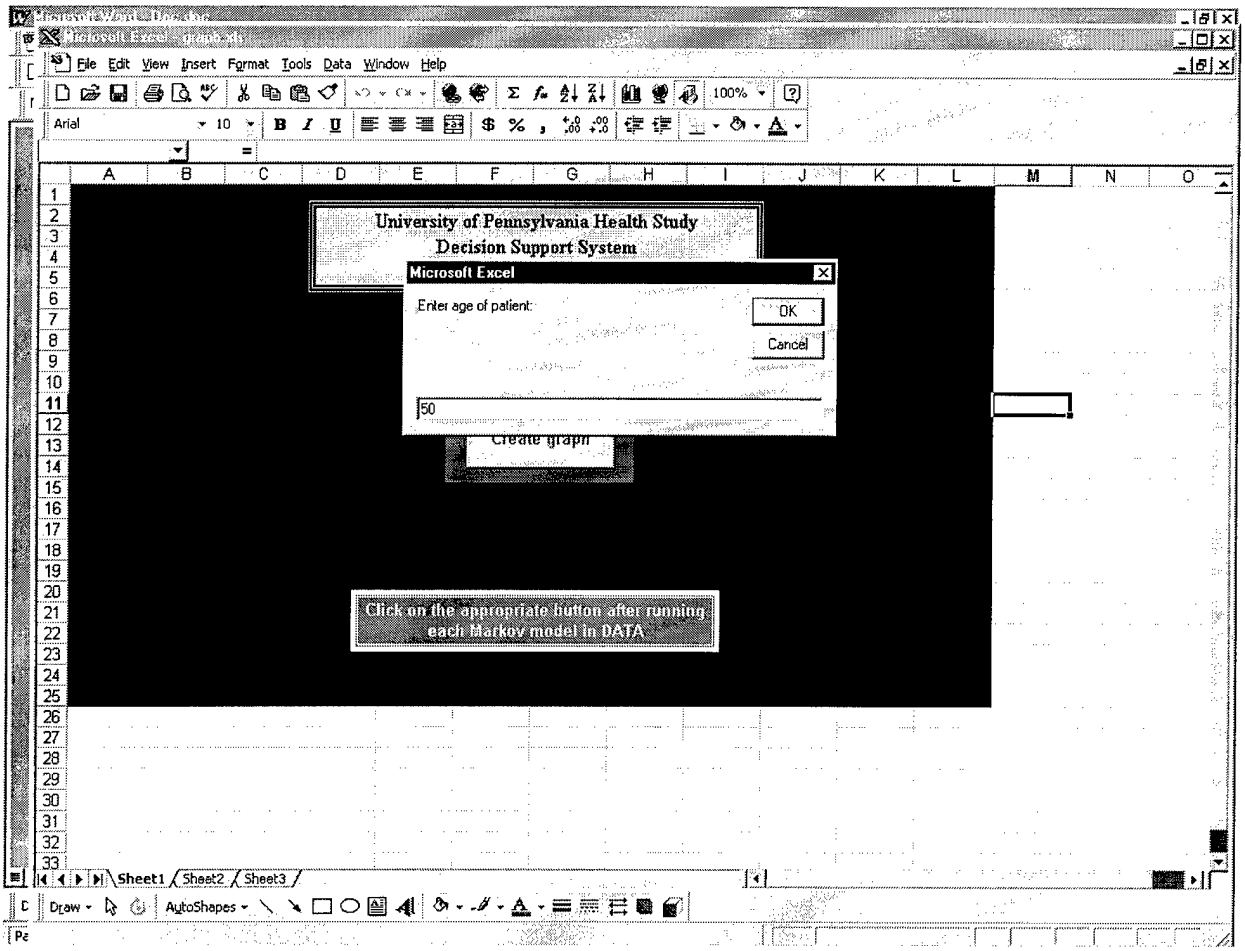



Fig. 16. After entering the patient's name, you will be prompted to enter her age; do so as an integer (no decimals or fractions) and click on the OK button.

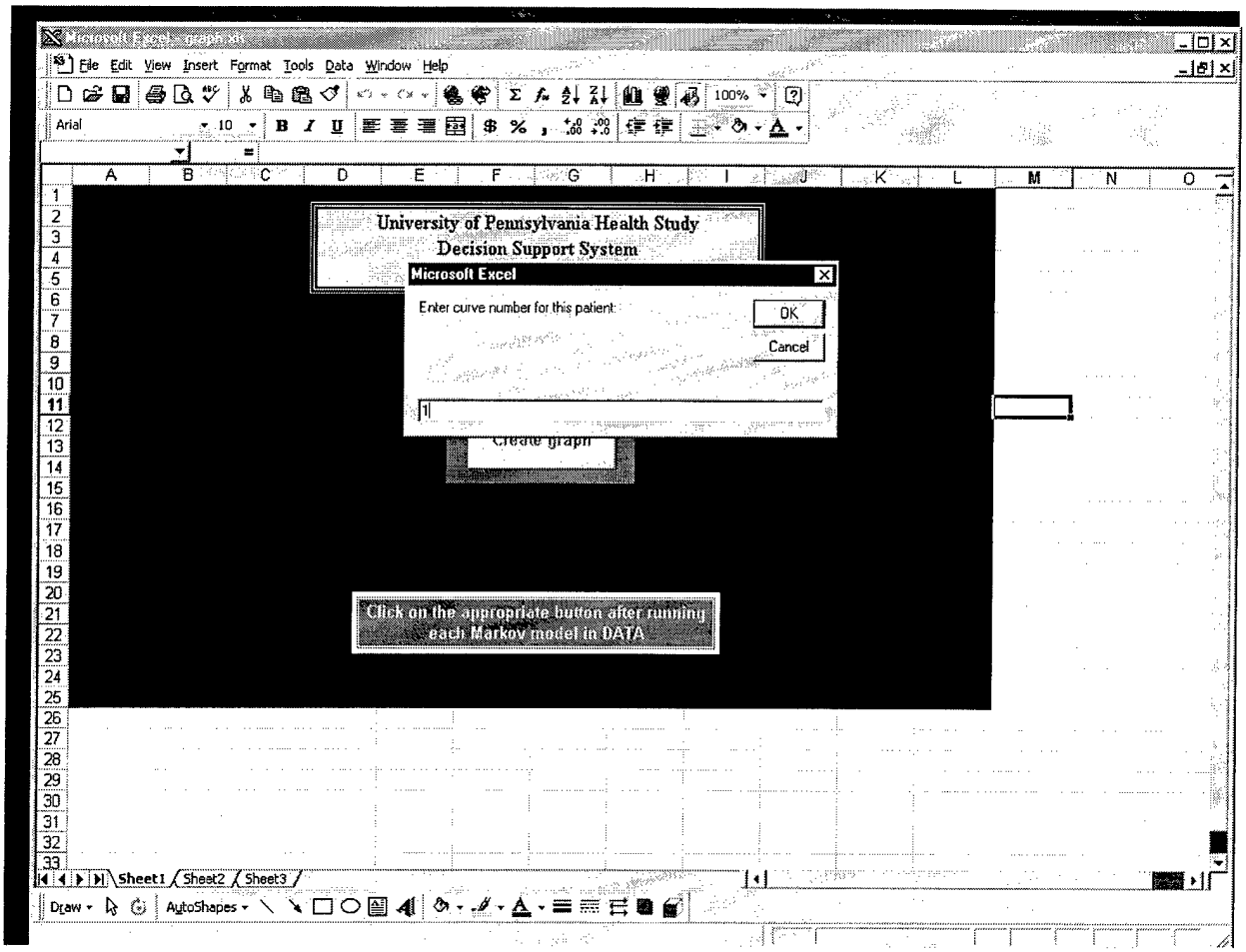



Fig. 17. You will then be prompted to enter the curve number for this patient. This can be a number between 1 and 10. Be sure to enter the curve numbers sequentially; do not skip any numbers, as each curve is saved as a separate file. In addition, do not use the same number twice.

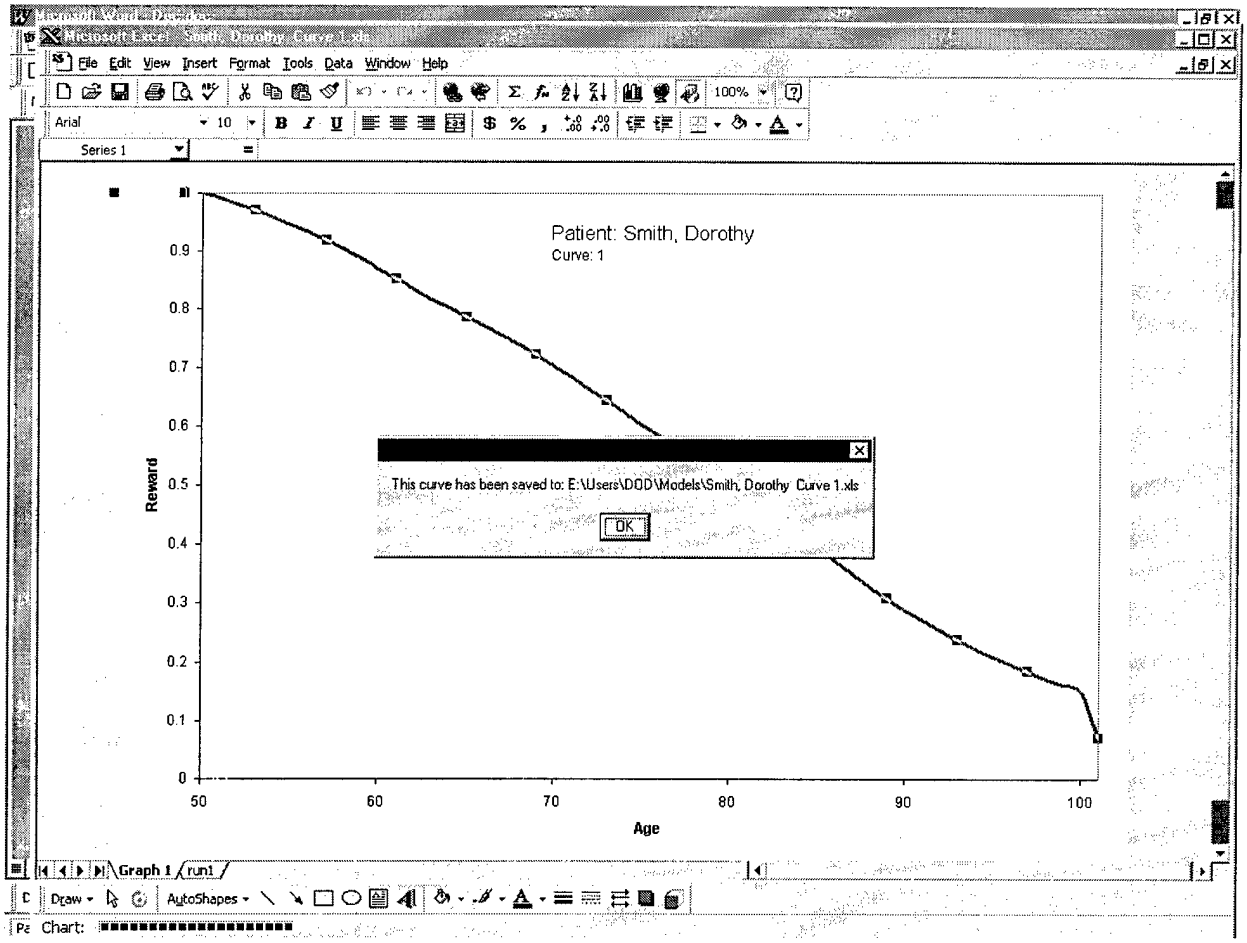



Fig. 18. After the graph is completed, the file will automatically be saved in D:\USERS\DOD\MODELS, with the filename: `lastname, firstname Curve n.xls`, where *n* is the number of the curve you entered in the screen shown in Fig. 17. The application will then close the graph window and return you to the opening screen of the Excel application (Fig. 14).

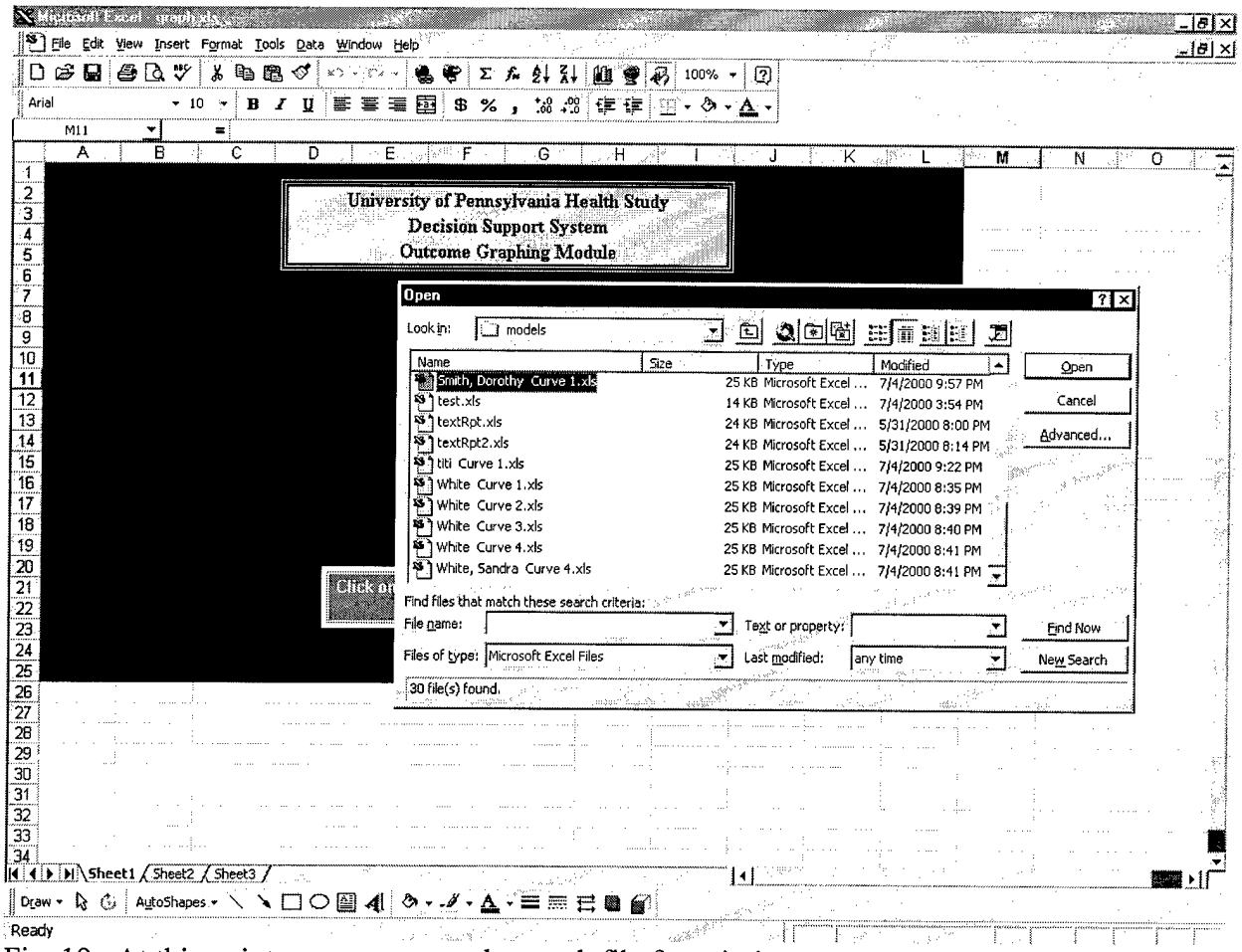



Fig. 19. At this point, you may open the graph file for printing.

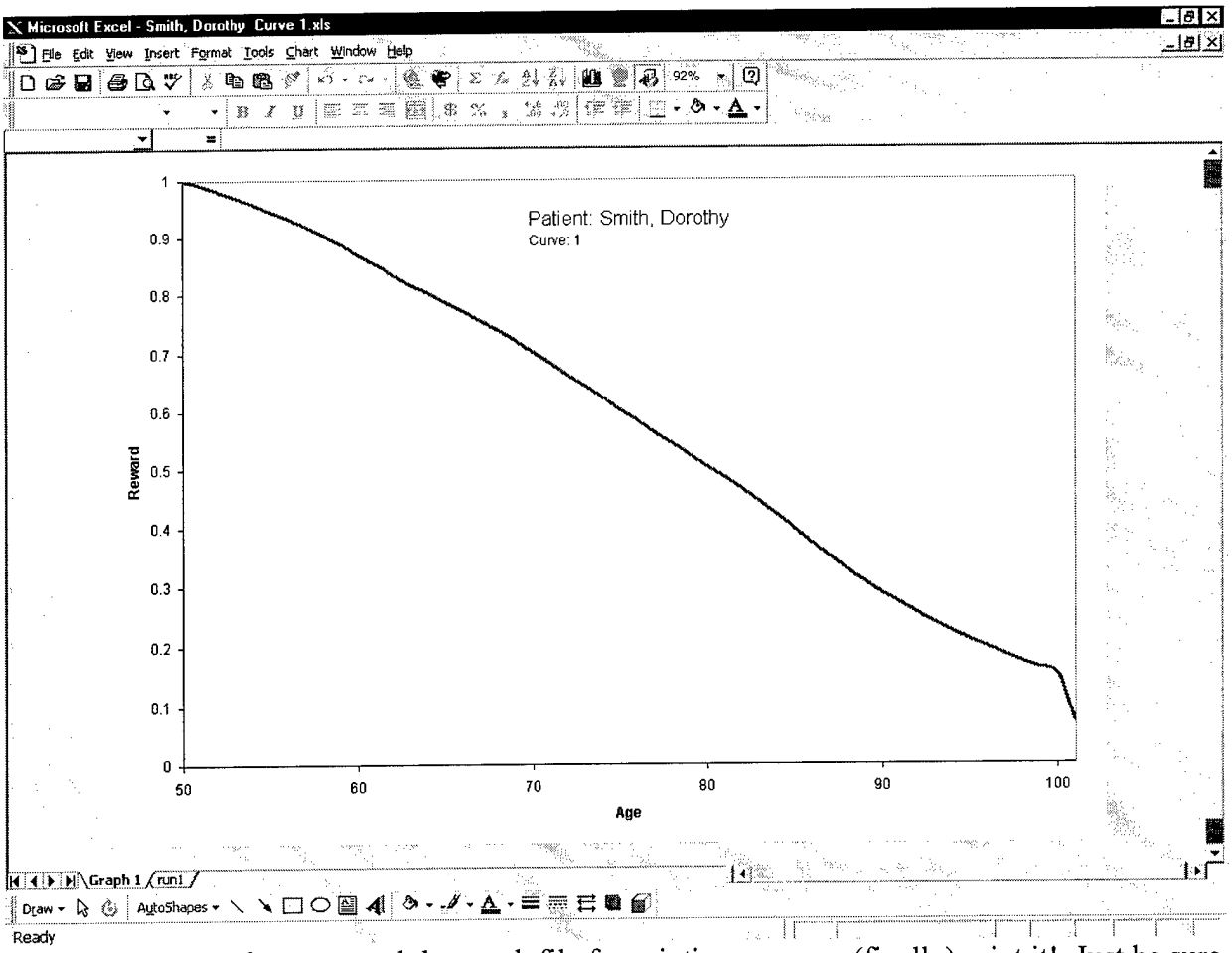



Fig. 20. Once you have opened the graph file for printing, you can (finally) print it! Just be sure your printer is turned on and has paper or transparency film loaded in the appropriate tray before you print. After you've completed the printing, you should close the graph files before entering another subject.

## Appendix C:
## Letter of Introduction to Study

*Introductory letter*

June 2, 2000

Dear Ms. ,

We would like to inform you of a study that you may become eligible for if you are found to carry a BRCA1 or BRCA2 mutation. Because managing your risk is a complex decision, with complicated information, we are constantly searching for new and better ways to help women with a BRCA mutation manage their health care options.

If you are found to carry a BRCA mutation, participation in this study will provide you access to more detailed information, not less, about your management options. This will be in addition to the counseling and medical care that you receive in the Breast Cancer Risk Evaluation Program, not in place of it. If you choose to participate, you will be asked to return for one additional counseling visit, for which there is no charge. As a token of our appreciation for your contribution, we would like to offer you a gift of $30. Once you have completed this visit, you will be contacted by phone in the following weeks to answer questions about what you thought of the information presented to you.

If you are found to have a BRCA1 or BRCA2 mutation, you are eligible to participate in this study. At your next visit, if you qualify, you will be asked if you would like to take part, and you will be given additional material to review. If you choose not to participate, your health care will in no way be compromised, as this is a voluntary study. If you have any questions, do not hesitate to call Genevieve FitzGerald at (215) 573-7275.

Sincerely,

Barbara Weber, M.D.

Katrina Armstrong, M.D.

Genevieve FitzGerald

## Appendix D:
## "Assessment of Risk Factors & Interest in Risk Reducing Options" Questionnaire

**Assessment of Risk Factors & Interest in Risk Reduction Options**

Please answer the following questions about your personal medical history as well as your interest in some procedures. Thank you.

1. Name_____

   Daytime Phone Number _____

2. Do you have high blood pressure? ☐ Yes ☐ No ☐ Not sure

   What was your most recent blood pressure reading (if known)? _____

   Do you take medication for high blood pressure? ☐ Yes ☐ No ☐ Not sure

3. Do you have diabetes? ☐ Yes ☐ No ☐ Not sure

4. Do you have high cholesterol? ☐ Yes ☐ No ☐ Not sure

   What was your most recent cholesterol reading (if known)? Total: _____

   LDL ("bad cholesterol"): _____

   HDL ("good cholesterol"):_____

   Do you take medication for high cholesterol? ☐ Yes ☐ No ☐ Not sure

5. Do you smoke cigarettes? ☐ Yes ☐ No ☐ Not sure

   *If yes:* How many cigarettes do you smoke a day? _____

6. Have you ever had a heart attack? ☐ Yes ☐ No ☐ Not sure

   Have you ever had angina? ☐ Yes ☐ No ☐ Not sure

   Do you take medication for heart disease? ☐ Yes ☐ No ☐ Not sure

7. Have you ever had breast cancer? ☐ Yes ☐ No ☐ Not sure

8. Have you ever had ovarian cancer? ☐ Yes ☐ No ☐ Not sure

Please answer the following questions about your interest in some options for managing your health.

These are on a scale from 1 to 5, 1=not at all to 5= extremely interested. Please rank your answers on this scale.

1. Are you interested in having a prophylactic mastectomy?

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| Not at all | | | | Extremely interested |

2. Are you interested in having a prophylactic oophorectomy?

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| Not at all | | | | Extremely interested |

3. Are you interested in taking tamoxifen (Nolvadex™) for cancer risk reduction?

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| Not at all | | | | Extremely interested |

4. Are you interested in taking hormone replacement therapy after menopause?

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| Not at all | | | | Extremely interested |

5. Are you interested in taking raloxifene (Evista™) after menopause?

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| Not at all | | | | Extremely interested |

## Appendix E:
## "Baseline Questionnaire"

## Woman's Health Decisions Study

Women found to have a BRCA1 or BRCA2 mutation are faced with many options for managing their risk of developing breast and/or ovarian cancer. These management options range from taking tamoxifen (Nolvadex™) to having a prophylactic mastectomy. In addition, women entering menopause may be faced with decisions about therapies such as hormone replacement therapy (HRT) or raloxifene (Evista™) that may also affect their risk of osteoporosis and heart disease.

Now, thinking about the choices that you may be facing, please look at the following comments other people have made. Please circle the number from 1 (strongly agree) to 5 (strongly disagree) that best shows how you feel about the decisions you are facing.

| | Strongly agree | Agree | Neither agree nor disagree | Disagree | Strongly disagree |
|---|---|---|---|---|---|
| These decisions are hard for me to make. | 1 | 2 | 3 | 4 | 5 |
| I'm unsure what to do in this situation. | 1 | 2 | 3 | 4 | 5 |
| It's clear which choices are best for me. | 1 | 2 | 3 | 4 | 5 |
| I'm aware of the management options I have to modify my risk. | 1 | 2 | 3 | 4 | 5 |
| I feel I know the benefits of the management options for my risk. | 1 | 2 | 3 | 4 | 5 |
| I am satisfied that I am adequately informed about the issues important to my decision. | 1 | 2 | 3 | 4 | 5 |
| I feel I know the risks and side effects of the management options for my risk. | 1 | 2 | 3 | 4 | 5 |
| I have the right amount of support from others in my decision making process. | 1 | 2 | 3 | 4 | 5 |
| I feel I am making an informed choice. | 1 | 2 | 3 | 4 | 5 |
| My decision shows what is most important for me. | 1 | 2 | 3 | 4 | 5 |
| I expect to stick with my decision. | 1 | 2 | 3 | 4 | 5 |
| I am satisfied that these are my decisions to make. | 1 | 2 | 3 | 4 | 5 |
| I expect to successfully carry out the decisions that I am making. | 1 | 2 | 3 | 4 | 5 |
| I am satisfied that my decisions are consistent with my personal values. | 1 | 2 | 3 | 4 | 5 |
| The decisions that I am making are the best possible for me personally. | 1 | 2 | 3 | 4 | 5 |

For the next set of items, please tell us whether you strongly disagree, somewhat disagree, neither agree nor disagree, somewhat agree, or strongly agree.

| | Strongly disagree | Somewhat disagree | Neither agree nor disagree | Somewhat agree | Strongly agree |
|---|---|---|---|---|---|
| The important medical decisions should be made by your doctor, not by you. | | | | | |
| You should go along with your doctor's advice even if you disagree with it. | | | | | |
| When hospitalized, you should not be making decisions about your own care. | | | | | |
| You should feel free to make decisions about everyday medical problems. | | | | | |
| If you were sick, as your illness became worse, you would want your doctor to take greater control. | | | | | |
| You should decide how frequently you need a check up. | | | | | |

Now suppose you developed a sore throat, stuffy nose, and cough that lasted for three days. You are about to call your doctor on the telephone. Who should make the following decisions? Should it be you alone, mostly you, the doctor and you equally, mostly the doctor, or the doctor alone?

| | You alone | Mostly you | Doctor & you equally | Mostly doctor | Doctor alone |
|---|---|---|---|---|---|
| Whether you should be seen by a doctor. | | | | | |
| Whether a chest x-ray should be taken. | | | | | |
| Whether you should try taking cough syrup. | | | | | |

Suppose you went to your doctor for a routine physical examination and he or she found that everything was all right except that your blood pressure was high (170/100). Who should make the following decisions? Should it be you alone, mostly you, the doctor and you equally, mostly the doctor, or the doctor alone?

| | You alone | Mostly you | Doctor & you equally | Mostly doctor | Doctor alone |
|---|---|---|---|---|---|
| When the next visit to check your blood pressure should be. | | | | | |
| Whether you should take time off from work to relax. | | | | | |
| Whether you should be treated with medication or diet. | | | | | |

Suppose you had an attack of severe chest pain that lasted for almost an hour, frightening you enough so that you went to the emergency room. In the emergency room the doctors discovered that you are having a heart attack. Your own doctor is called and you are taken up to the intensive care unit. Who should make the following decisions? Should it be you alone, mostly you, the doctor and you equally, mostly the doctor or the doctor alone?

| | You alone | Mostly you | Doctor & you equally | Mostly doctor | Doctor alone |
|---|---|---|---|---|---|
| How often the nurses should wake you up to check your temperature and blood pressure. | | | | | |
| Whether you may have visitors aside from your immediate family. | | | | | |
| Whether a cardiologist should be consulted. | | | | | |

For the next set of items, please tell us whether you strongly disagree, somewhat disagree, neither agree nor disagree, somewhat agree, or strongly agree.

| | Strongly disagree | Somewhat disagree | Neither agree nor disagree | Somewhat agree | Strongly agree |
|---|---|---|---|---|---|
| As you become sicker you should be told everything about your illness. | | | | | |
| You should understand completely what is happening inside your body as a result of your illness. | | | | | |
| Even when news is bad, you should be well informed. | | | | | |
| Your doctor should explain the purpose of your laboratory tests. | | | | | |
| You should be given information only when you ask for it. | | | | | |
| It is important for you to know all the side effects of your medication. | | | | | |
| Information about your illness is as important as your treatment. | | | | | |
| When there is more than one method to treat a problem, you should be told about each one. | | | | | |

Please check the appropriate box next to the statement about you during the past week:

| | Rarely/none of the time (<1/ day) | Occasionally/ little of the time (1-2 days) | Some/ moderate amount of time (3-4 days) | Most/ all of the time (5-7 days) |
|---|---|---|---|---|
| I was bothered by things that don't usually bother me. | | | | |
| I did not feel like eating; my appetite was poor. | | | | |
| I felt that I could not shake the blues even with help from my family and friends. | | | | |
| I felt that I was just as good as other people. | | | | |
| I had trouble keeping my mind on what I was doing. | | | | |
| I felt depressed. | | | | |
| I felt that everything that I did was an effort. | | | | |
| I felt hopeful about the future. | | | | |
| I thought that my life had been a failure. | | | | |
| I felt fearful. | | | | |
| My sleep was restless | | | | |
| I was happy. | | | | |
| I talked less than usual. | | | | |
| I felt lonely. | | | | |
| People were unfriendly. | | | | |
| I enjoyed life. | | | | |
| I had crying spells. | | | | |
| I felt sad. | | | | |
| I felt that people dislike me. | | | | |
| I could not get "going." | | | | |

The next questions ask about what you think about your risk of developing cancer or heart disease.

What do you believe is your chance of developing breast cancer by age 70 if you have yearly mammograms, but choose not to have prophylactic surgery, take tamoxifen, or take HRT (Hormone Replacement Therapy) or raloxifene after menopause?_____%

...How about if you do have a prophylactic mastectomy? _____%

...How about if you do have a prophylactic oophorectomy? _____%

...How about if you do take tamoxifen? _____%

...How about if you do take HRT after menopause? _____%

...How about if you do raloxifene after menopause? _____%

What do you believe your chance of developing ovarian cancer is by age 70 if you choose not to have a prophylactic oophorectomy? _____%

...How about if you do have a prophylactic oophorectomy? _____%

What do you believe your chance of developing heart disease by age 70 is if you choose not to take HRT or raloxifene at the onset of menopause? _____%

...How about if you do take HRT at the onset of menopause? _____%

...How about if you do take raloxifene at the onset of menopause? _____%

The next questions are about comments made by people concerned about breast cancer (BC), and/or ovarian cancer (OC). Please tell us how frequently these comments were true for you during the past week.

| During the past week: | Not at all | Rarely | Sometimes | Often |
|---|---|---|---|---|
| You thought about BC and/or OC when you didn't mean to. | | | | |
| You had trouble falling asleep or staying asleep because of pictures or thoughts about BC and/or OC that came into your mind. | | | | |
| You had waves of strong feelings about BC and/or OC. | | | | |
| You had dreams about BC and/or OC. | | | | |
| Pictures about BC and/or OC popped into your mind. | | | | |
| Any reminder brought back feelings about BC and/or OC. | | | | |

Please answer the following questions about some management options that you may have heard of.

**Prophylactic Mastectomy (preventative removal of the breasts)**

Have you had a prophylactic mastectomy? ☐ Yes ☐ No ☐ Not sure

If not, are you thinking about having a prophylactic mastectomy:

In the next 6 months? ☐ Yes ☐ No ☐ Not sure

In the next month? ☐ Yes ☐ No ☐ Not sure

**Prophylactic Oophorectomy (preventative removal of the ovaries)**

Have you had a prophylactic oophorectomy? ☐ Yes ☐ No ☐ Not sure

If not, are you thinking about having a prophylactic oophorectomy:

In the next 6 months? ☐ Yes ☐ No ☐ Not sure

In the next month? ☐ Yes ☐ No ☐ Not sure

**Tamoxifen (Nolvadex™) for breast cancer prevention**

Are you taking tamoxifen? ☐ Yes ☐ No ☐ Not sure

If not, are you thinking about taking tamoxifen:

In the next 6 months? ☐ Yes ☐ No ☐ Not sure

In the next month? ☐ Yes ☐ No ☐ Not sure

**Hormone Replacement Therapy (HRT) after menopause**

Are you taking HRT? ☐ Yes ☐ No ☐ Not sure

If not, are you thinking about taking HRT:

In the next 6 months? ☐ Yes ☐ No ☐ Not sure

In the next month? ☐ Yes ☐ No ☐ Not sure

At the time of menopause? ☐ Yes ☐ No ☐ Not sure

**Raloxifene (Evista™) after menopause**

Are you taking raloxifene? ☐ Yes ☐ No ☐ Not sure

If not, are you thinking about taking raloxifene:

In the next 6 months? ☐ Yes ☐ No ☐ Not sure

In the next month? ☐ Yes ☐ No ☐ Not sure

At the time of menopause? ☐ Yes ☐ No ☐ Not sure

## Appendix F:
## "Outcomes of Women's Health Study" Questionnaire

## Outcomes of Woman's Health Decisions Study

Women found to have a BRCA1 or BRCA2 mutation are faced with many options for managing their risk of developing breast and/or ovarian cancer. You have read and heard about many of your management options, and I would like you to think carefully about the process that led to your decision of what method to use in managing your health as I ask you these questions.

Now, thinking about the choices that you have made, please listen to the following comments some people make. Tell me whether you strongly agree, agree, neither agree nor disagree, disagree, or strongly disagree for each statement that I read you.

| | Strongly agree | Agree | Neither agree nor disagree | Disagree | Strongly disagree |
|---|---|---|---|---|---|
| 1.These decisions are hard for me to make. | 1 | 2 | 3 | 4 | 5 |
| 2.I'm unsure what to do in this situation. | 1 | 2 | 3 | 4 | 5 |
| 3. It's clear which choices are best for me. | 1 | 2 | 3 | 4 | 5 |
| 4. I'm aware of the management options I have to modify my risk. | 1 | 2 | 3 | 4 | 5 |
| 5. I feel I know the benefits of the management options for my risk. | 1 | 2 | 3 | 4 | 5 |
| 6. I am satisfied that I am adequately informed about the issues important to my decision. | 1 | 2 | 3 | 4 | 5 |
| 7. I feel I know the risks and side effects of the management options for my risk. | 1 | 2 | 3 | 4 | 5 |
| 8. I have the right amount of support from others in my decision making process. | 1 | 2 | 3 | 4 | 5 |
| 9. I feel I am making an informed choice. | 1 | 2 | 3 | 4 | 5 |
| 10. My decision shows what is most important for me. | 1 | 2 | 3 | 4 | 5 |
| 11. I expect to stick with my decision. | 1 | 2 | 3 | 4 | 5 |
| 12. I am satisfied that these are my decisions to make. | 1 | 2 | 3 | 4 | 5 |
| 13. I expect to successfully carry out the decisions that I am making. | 1 | 2 | 3 | 4 | 5 |
| 14. I am satisfied that my decisions are consistent with my personal values. | 1 | 2 | 3 | 4 | 5 |
| 15. The decisions that I am making are the best possible for me personally. | 1 | 2 | 3 | 4 | 5 |

Please tell me how many times you have thought about each statement during the past week:

Was it Rarely/None of the time, Occasionally, Somewhat, or most of the time?

| | Rarely/none of the time (<1/ day) | Occasionally/ little of the time (1-2 days) | Some/ moderate amount of time (3-4 days) | Most/ all of the time (5-7 days) |
|---|---|---|---|---|
| 16. I was bothered by things that don't usually bother me. | | | | |
| 17.I did not feel like eating; my appetite was poor. | | | | |
| 18. I felt that I could not shake the blues even with help from my family and friends. | | | | |
| 19. I felt that I was just as good as other people. | | | | |
| 20. I had trouble keeping my mind on what I was doing. | | | | |
| 21. I felt depressed. | | | | |
| 22. I felt that everything that I did was an effort. | | | | |
| 23. I felt hopeful about the future. | | | | |
| 24. I thought that my life had been a failure. | | | | |
| 25. I felt fearful. | | | | |
| 26. My sleep was restless | | | | |
| 27. I was happy. | | | | |
| 28. I talked less than usual. | | | | |
| 29. I felt lonely. | | | | |
| 30. People were unfriendly. | | | | |
| 31. I enjoyed life. | | | | |
| 32. I had crying spells. | | | | |
| 33. I felt sad. | | | | |
| 34. I felt that people dislike me. | | | | |
| 35. I could not get "going." | | | | |

The next questions ask about what you think about your risk of developing cancer or heart disease. Give me a percent between 0 and 100%.

36. What do you believe that your chance of developing breast cancer is by age 70 if you have yearly mammograms, but choose not to have prophylactic surgery, take tamoxifen, or take HRT (Hormone Replacement Therapy) or raloxifene after menopause in a percentage? _____%
37. ...How about if you do have a prophylactic mastectomy? _____%
38. ...How about if you do have a prophylactic oophorectomy? _____%
39. ...How about if you do take tamoxifen? _____%
40. ...How about if you do take HRT after menopause? _____%
41. ...How about if you do raloxifene after menopause? _____%

42. What do you believe your chance of developing ovarian cancer is by age 70 if you choose not to have a prophylactic oophorectomy in a percentage? _____%
43. ...How about if you do have a prophylactic oophorectomy? _____%

44. What do you believe your chance of developing heart disease by age 70 is if you choose not to take HRT or raloxifene at the onset of menopause in a percentage? _____%
45. ...How about if you do take HRT at the onset of menopause? _____%
46. ...How about if you do take raloxifene at the onset of menopause? _____%

The next questions are about comments made by people concerned about breast cancer (BC), and/or ovarian cancer (OC). Please tell us how frequently these comments were true for you during the past week, not at all, rarely, somewhat, or often.

| During the past week: | Not at all | Rarely | Sometimes | Often |
|---|---|---|---|---|
| 47. You thought about BC and/or OC when you didn't mean to. | | | | |
| 48. You had trouble falling asleep or staying asleep because of pictures or thoughts about BC and/or OC that came into your mind. | | | | |
| 49. You had waves of strong feelings about BC and/or OC. | | | | |
| 50. You had dreams about BC and/or OC. | | | | |
| 51. Pictures about BC and/or OC popped into your mind. | | | | |
| 52. Any reminder brought back feelings about BC and/or OC. | | | | |

Please answer the following questions about some management options that you may have heard of.

Answer yes, no, or not sure.

**Prophylactic Mastectomy (preventative removal of the breasts)**

53. Have you had a prophylactic mastectomy? ☐ Yes ☐ No ☐ Not sure

If not, are you thinking about having a prophylactic mastectomy:

53a. In the next 6 months? ☐ Yes ☐ No ☐ Not sure

53b. In the next month? ☐ Yes ☐ No ☐ Not sure

**Prophylactic Oophorectomy (preventative removal of the ovaries)**

54. Have you had a prophylactic oophorectomy? ☐ Yes ☐ No ☐ Not sure

If not, are you thinking about having a prophylactic oophorectomy:

54a. In the next 6 months? ☐ Yes ☐ No ☐ Not sure

54b. In the next month? ☐ Yes ☐ No ☐ Not sure

**Tamoxifen (Nolvadex™) for breast cancer prevention**

55.Are you taking tamoxifen? ☐ Yes ☐ No ☐ Not sure

If not, are you thinking about taking tamoxifen:

55a. In the next 6 months? ☐ Yes ☐ No ☐ Not sure

55b. In the next month? ☐ Yes ☐ No ☐ Not sure

**Hormone Replacement Therapy (HRT) after menopause**

56. Are you taking HRT? ☐ Yes ☐ No ☐ Not sure

If not, are you thinking about taking HRT:

56a. In the next 6 months? ☐ Yes ☐ No ☐ Not sure

56b. In the next month? ☐ Yes ☐ No ☐ Not sure

56c. At the time of menopause? ☐ Yes ☐ No ☐ Not sure

**Raloxifene (Evista™) after menopause**

57. Are you taking raloxifene? ☐ Yes ☐ No ☐ Not sure

If not, are you thinking about taking raloxifene:

57a. In the next 6 months? ☐ Yes ☐ No ☐ Not sure

57b. In the next month? ☐ Yes ☐ No ☐ Not sure

57c. At the time of menopause? ☐ Yes ☐ No ☐ Not sure

## Appendix G:
## "Using survival curve comparisons to inform patient decision making: Can a training exercise improve understanding?"

# Using Survival Curve Comparisons to Inform Patient Decision Making: Can a Training Exercise Improve Understanding?

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## ABSTRACT

**Background:** Patients are often faced with medical decisions that involve outcomes that occur and change over time. Survival curves are a promising communication tool for patient decision support because they present information about the probability of an outcome over time in a simple graphic format. However, previous studies of survival curves did not measure comprehension, used face-to-face explanations and focused on a VA population.

**Methods:** In this study, 246 individuals awaiting jury duty at the Philadelphia City courthouse were randomized to receive one of two questionnaires. The control group received a questionnaire describing two hypothetical treatments and a graph with two survival curves showing the outcomes of the treatments. The training group received the same questionnaire preceded by a training exercise asking questions about a graph containing a single curve. Subjects' ability to interpret survival from a curve, ability to calculate change in survival over time and treatment preference were measured.

**Results:** The training group was significantly more likely to accurately interpret survival from a two curve graph (83% vs 74% accurate, p=0.03). All subjects had difficulty calculating change in survival between two time points (55% accurate in both groups). Use of a training exercise did not affect treatment preference.

**Conclusion:** The majority of the general public can understand self-administered survival curves. This understanding is improved by a single curve training exercise. However, a significant proportion of the general public cannot calculate change in survival over time. Further research is necessary to determine the effectiveness of survival curves in improving risk communication and patient decision making.

## INTRODUCTION

Patients are often faced with medical decisions that involve outcomes that occur and change over time. Choosing an aggressive treatment, such as surgery, over a less aggressive treatment may trade a short-term increase in mortality for a long-term increase in survival. In many situations, in order to make an informed decision, a patient must understand both the conditional probabilities of an outcome and how those probabilities change over time. How best to present this complex information to help patients make decisions that better reflect their true preferences is not clear. Extensive numerical information may overwhelm a patient's ability to process and understand it. (1,2) But, presenting limited information, for example survival probabilities at two or three time points, may bias decisions. (3,4)

Survival curves may overcome these problems by presenting information about the probability of an outcome over time in a simple graphic format without extensive numeric data. Several studies have used survival curves to convey information about treatment choices to patients in face-to-face discussions.(5-8) These studies focused on the effects of alternative framing on treatment preference. We have chosen to extend this research for several reasons. First, recent literature suggests patients may have difficulty understanding even simple probabilities.(8,9) Prior studies did not measure subjects' ability to understand survival curve information - raising the possibility that understanding of curves may actually be insufficient for effective communication. Second, previous survival curve studies were conducted using face-to-face interviews, raising questions regarding whether patients can understand self-administered survival curves. These questions are important because many decision and communication

aids now being developed are self-administered.(10,11) If survival curves can be understood when self-administered, their potential application as a communication aid will be considerably broader. Finally, participants for the prior studies were drawn exclusively from Veterans Administration clinics and may not be generalizable to other patient populations.

The objectives of our study were to determine: (1) if the general public can understand survival curves when presented in a self-administered format; (2) if understanding of a graph containing two curves is worse than understanding of a graph containing a single curve; and (3) if understanding of a graph containing a two curve comparison improves with a single curve training exercise.

## METHODS

### Study Design

We randomized study subjects to receive one of two questionnaires. The control group received a questionnaire describing a hypothetical health condition with two possible treatments and a graph with two survival curves showing the outcomes of the treatments. The training group received the same questionnaire preceded by a training exercise asking questions about a graph containing a single curve. The study protocol was approved by the Human Subjects Committee of the Institutional Review Board at the University of Pennsylvania.

**Study Setting and Participants**

Prospective jurors awaiting jury selection at the Philadelphia City Courthouse were offered a candy bar to complete the study questionnaire. In Philadelphia, individuals are randomly selected for jury duty from voter registration and drivers license records.

**Intervention**

Each participant was given a self-administered questionnaire that included a brief explanation of survival curves, a graph containing two survival curves illustrating the outcomes of two hypothetical treatments and outcome measurement questions (see below). The brief explanation read:

> *We will show you a graph of survival curves. A survival curve is a picture that shows how long people live after being diagnosed with for a disease. You will notice there are different curves on the graph. Each curve shows how many people survive using the different treatments for the disease. Survival curves are shown to patients to help them understand their disease and to decide which treatment option is best for them.*
>
> *The graph below shows how many people survive after either having heart surgery or being put on heart medication. At year 0, 100 patients were started on medication and 100 patients had surgery. The curve marked by the squares shows the patients who had surgery. The curve marked by the circles shows the patients who are on medication. The curves show how many people are alive every five years after having surgery or being put on medication.*

For participants randomized to the intervention arm, the questionnaire also contained an additional page with an introductory training exercise that presented a single survival curve for a hypothetical condition and asked several questions about the information contained in the single curve (Appendix A). The correct answers to these questions were not provided.

**Outcome Measures**

The primary outcome measure was comprehension of the information contained in the figure containing two survival curves. We asked subjects both to interpret survival rates at a single time point (e.g., how many people having surgery are alive at year 20?) and change in survival over a specific time period (e.g., how many people having surgery died between year 20 and year 40?) for each of the two curves. Care was taken to ensure that each question asked about points on the survival curve that could be read easily and unambiguously from the scale provided, e.g. 50 people alive instead of 47 people alive. In addition, to determine if the addition of a training exercise affected hypothetical treatment preferences, we asked each subject which therapy they would choose.

**Statistical Analysis**

Baseline characteristics of the two groups (single curve training exercise vs. no training exercise) were compared using chi-square tests for categorical variables and t-tests for continuous variables. For each subject, separate accuracy scores were generated for the ability to interpret the number alive at a given point (five questions) and the ability to calculate change in survival (two questions), by dividing the number of questions answered correctly by the total number of questions. Because these scores were not

normally distributed, they were compared between groups using the Wilcoxon rank-sum test. In addition, for the group that received the single curve training exercise, accuracy scores were generated for the single curve graph and compared within subject to their accuracy scores for the double curve graph using the Wilcoxon rank-sum test.

## RESULTS

Of the 246 subjects who completed the questionnaire, 120 received the training intervention and 146 did not. The two groups were similar in age, gender, education and ethnicity. (Table 1)

Among the intervention group, understanding of the single curve was greater than understanding of the double curve. For example, ability to interpret the number of people alive at a point in time declined from 92% to 83% ($p=0.006$), and ability to calculate the change in survival over time declined from 67% to 55% ($p=0.04$).

Despite the decline in understanding from a single curve graph to a two curve graph, the intervention group's understanding of a graph containing two curves exceeded the control group, which did not receive the single curve training exercise. (Table 2) Over ninety percent of subjects in the intervention group could accurately interpret survival at a single point in time from a survival curve compared to only 74% of subjects in the control group. However, only a little over half of subjects in either group could calculate change in survival over time. Use of a training exercise did not affect hypothetical treatment preferences with approximately three-quarters of subjects in both groups preferring surgery.

## DISCUSSION

Our results suggest that the majority of the general public can understand survival at a point in time from a graph comparing two survival curves and that this understanding is improved by a single curve training exercise. However, almost half of our subjects could not calculate a change in survival over time from a survival curve – a task that requires both interpreting survival from a curve and subtraction.

This study adds important information to the literature on risk communication. Survival curves are a potentially powerful tool for risk communication because they provide information about outcomes at many points in time without using extensive numeric data. Prior studies have used survival curves to demonstrate that patients focus on different portions of survival curves than physicians, that order of presentation affects treatment preferences, that length of the explanation affects treatment preferences and that patients are willing to trade a short term increase in mortality for long term increase in survival.(4-7) To our knowledge, our study is the first to demonstrate that the general public can calculate survival from a survival curve even in the absence of a face-to-face explanation. Importantly, however, our study raises significant concerns about the ability of the general public to calculate differences in survival from a survival curve. Such comparisons may be an important component of the cognitive tasks necessary for patients to use survival curve information to aid their decision making.

The effect of training on the ability to perform cognitive tasks has been well established in the cognitive psychology literature.(13-18) In general, training can be categorized as domain specific or transferable. Domain specific training involves

exercises specific to the task of interest and is theorized to result in the adoption of concrete rules that apply only to the particular task.(18) Transferable training proposes that reasoning can be taught that can be used for problem solving in diverse settings. (13-17) Our study used domain specific training (use of survival curve exercise to teach interpretation of survival curves). It is possible that training in survival curves may transfer to other tasks involving understanding probabilities.

Our study has several limitations. Although the juror pool is highly representative of the population of the city of Philadelphia, it is less representative of other segments of the US population. We chose to use jurors rather than patients because of concerns about patients misinterpreting the data from the hypothetical situations as reflections of their own health status. Because of the nature of our experimental study design, we were able to compare only two alternative formats of our questionnaire. Clearly, the format of each part of the questionnaire from the introduction to the outcome questions may affect the results. Our results are not necessarily generalizable to other formats.

Communicating risk information is difficult. Survival curves offer a potentially powerful graphic communication aid that may overcome some of the limitations of numeric data. However, for survival curves to help patients make complex decisions, patients must be able both to understand the information contained in a survival curve and to compare pairs or other combinations of curves. Although the ability of the general public to interpret survival from a survival curve suggests that patients can understand a single curve, the relative inability of the general public to calculate change in survival raises concerns about the ability of patients to use survival curve comparisons to inform their choices.

**Table 1. Subject Characteristics**

| | Training Exercise | Control | p-value |
|---|---|---|---|
| Mean Age (range) | 39.7 | 39.7 | 0.51 |
| Women (%) | 67 | 67 | 0.85 |
| Caucasian (%) | 55 | 47 | 0.24 |
| African-American (%) | 40 | 44 | 0.12 |
| Mean Years of Education (range) | 13.8 | 14.0 | 0.78 |

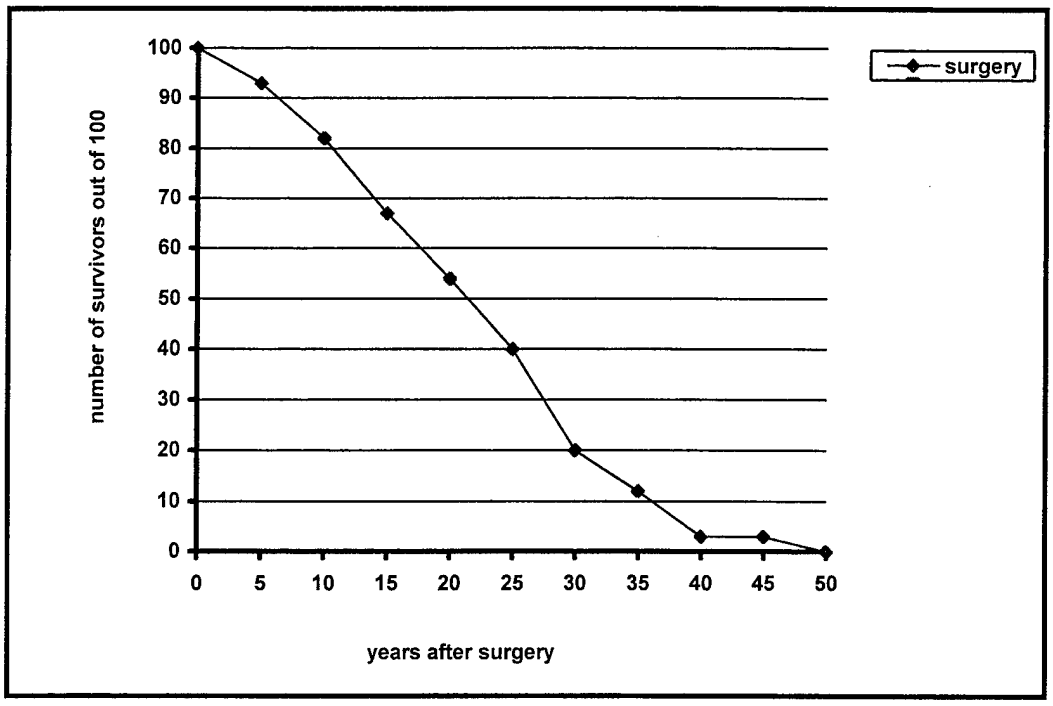
**Table 2. Comprehension of Double Curve Presentation**

| | Training Exercise | Control | p-value |
|---|---|---|---|
| Number alive* | 0.83 | 0.74 | 0.03 |
| Change in number alive* | 0.55 | 0.55 | 0.89 |
| Choice# | 0.79 | 0.76 | 0.48 |

* Proportion of subjects who answered questions accurately
# Proportion of subjects who preferred surgery

# Appendix

## Single Curve Training Exercise




The above graph shows the number of people who survive after having heart surgery. It begins with 100 patients having surgery at year 0. The graph shows how many people are alive every five years after having surgery. For example, twenty years after surgery, 54 people are still alive. Please answer the following questions using the above graph.

1. How many people are alive at year 0? _____
2. How many people are alive at year 25? _____
3. How many people died between year 0 and year 30? _____
4. How many people are alive at year 50? _____
5. Did more people die between years 0 and 5 or between years 10 and 15?_____

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## Appendix H:
## "Assessing the Risk of Breast Cancer"

Review Article

*Primary Care*

# Assessing the Risk of Breast Cancer

Katrina Armstrong, M.D., Andrea Eisen, M.D., and Barbara Weber, M.D.

EACH year in the United States, breast cancer is diagnosed in more than 170,000 women.[1] Despite this substantial burden of disease, however, assessment of breast-cancer risk has received very little attention outside the oncology clinic.[2,3] In primary care, the main result of the recognition of individual variation in breast-cancer risk is the use of age to determine recommendations regarding mammography (older age is a strong risk factor for breast cancer).[4]

Recent developments in the ability to predict and alter breast-cancer risk warrant a new look at the role of assessment of this risk in primary care. Physicians must become adept at evaluating breast-cancer risk and counseling women about its effect on medical decisions. To provide both the rationale and the tools for evaluating breast-cancer risk, this article examines the effects of breast-cancer risk on medical decisions and explains current methods of assessing risk.

## WHY EVALUATE BREAST-CANCER RISK?

Several important medical decisions may be affected by a woman's underlying risk of breast cancer. These decisions include whether to use postmenopausal hormone-replacement therapy, at what age to begin mammographic screening, whether to use tamoxifen to prevent breast cancer, and whether to perform prophylactic mastectomy to prevent breast cancer.

From the Department of Medicine (K.A., A.E., B.W.) and the Center for Clinical Epidemiology and Biostatistics (K.A.), University of Pennsylvania School of Medicine; the University of Pennsylvania Cancer Center (K.A., A.E., B.W.); and the Leonard Davis Institute of Health Economics, University of Pennsylvania (K.A.) — all in Philadelphia. Address reprint requests to Dr. Armstrong at 1233 Blockley Hall, 423 Guardian Dr., Philadelphia, PA 19104-6021, or at karmstro@mail.med.upenn.edu.



### Decisions about Postmenopausal Hormone-Replacement Therapy

Observational studies suggest that postmenopausal hormone-replacement therapy halves the risk of coronary heart disease and osteoporosis but increases the risk of breast cancer by 30 to 40 percent.[5-7] Because the reductions in the risk of coronary heart disease and osteoporosis are greater than the increase in the risk of breast cancer, and because the average woman's risk of dying from coronary heart disease is much greater than her risk of dying from breast cancer, most experts argue that the benefits of hormone-replacement therapy outweigh the risks in most women.[8,9]

However, the balance between the risks and the benefits of hormone-replacement therapy may shift for women who have a substantially increased risk of breast cancer. Although the relative risk associated with hormone-replacement therapy does not appear to be higher in women with a family history of breast cancer, decision analysis suggests that the absolute benefit of hormone-replacement therapy (measured as the net increase in life expectancy) falls as the risk of breast cancer increases.[9-12] In one such model, hormone-replacement therapy no longer increased life expectancy for women with a lifetime breast-cancer risk above 30 percent and an average risk of cardiac events. Although the number of postmenopausal women with such a high risk of breast cancer is small, assessment of breast-cancer risk provides valuable information for use in making decisions about hormone-replacement therapy.[13-15] Furthermore, assessment of breast-cancer risk may reassure the larger number of women with a risk below this threshold that the benefits of hormone-replacement therapy outweigh its risks.

The number of women who use individual assessments of breast-cancer risk to make decisions about postmenopausal therapy may increase as alternatives to hormone-replacement therapy become available. Raloxifene, a selective estrogen-receptor modulator, provides less protection against coronary heart disease and osteoporosis than hormone-replacement therapy, but it may reduce the risk of breast cancer.[16-18] Because of these trade-offs in risk reduction, it is likely that breast-cancer risk will be an important factor in determinations of the expected relative benefits of raloxifene and hormone-replacement therapy. As a woman's risk of breast cancer increases, the relative benefit of raloxifene as compared with hormone-replacement therapy will increase. A recent decision analysis suggests that if the goal is to increase life expectancy, raloxifene is the preferred alternative for postmenopaus-

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al women who are at substantially increased risk of breast cancer.[10]

### Decisions about the Use of Mammography for Women 40 to 49 Years of Age

The routine use of screening mammography in women 50 years old or older reduces mortality from breast cancer by approximately one third.[19] This reduction comes without substantial risks and at an acceptable economic cost.[20,21] However, the use of screening mammography is more controversial in women under the age of 50, for several reasons. First, because breast density is generally higher in younger women, screening mammography is less likely to detect early breast cancer at a curable stage. Thus, the reduction in mortality from breast cancer is lower.[22] Second, also because of their higher breast density, screening mammography in younger women results in more false positive tests, with the associated anxiety and unnecessary biopsies.[23] Third, because women under the age of 50 are less likely to have breast cancer, fewer women in this age group will benefit from screening.[1] Fourth, the lower incidence of breast cancer among these women increases the cost of mammography per year of life saved to more than $100,000.[24] Expert panels have concluded that, on a population basis, the benefits of screening mammography in women between 40 and 49 years of age still outweigh the risks. The goal of maximizing the benefit of mammography while minimizing its risks remains uncontested.[25,26]

Although the assessment of breast-cancer risk cannot improve the efficacy of mammography, targeting mammography to women at higher risk of breast cancer can improve the balance of risks and benefits.[27-29] Among women at higher risk, mammography results in a greater absolute decrease in the risk of death from breast cancer and is more cost effective. A higher prevalence of disease results in a lower proportion of false positive tests. In one analysis of women 40 to 49 years of age, an abnormal mammogram was more than three times as likely to be associated with cancer in a woman with a family history of cancer as in a woman without a family history of cancer.[23]

Several authors have published risk-based recommendations for mammographic screening.[28,29] A recent article focusing on women 40 to 49 years of age described procedures to determine whether a woman's risk equaled that of a 50-year-old woman without risk factors for breast cancer.[29] Because the benefit of mammography is widely accepted to exceed the risks for all 50-year-old women, these procedures can be used to determine whether a younger woman's risk of breast cancer meets this criterion.

### Decisions about the Use of Tamoxifen for the Prevention of Breast Cancer

Tamoxifen, a selective estrogen-receptor modulator, is the first drug shown to reduce the incidence of breast cancer in healthy women. The Breast Cancer Prevention Trial randomly assigned more than 13,000 women with a five-year risk of breast cancer of 1.7 percent or more to tamoxifen or placebo.[30] After a mean follow-up period of four years, tamoxifen had reduced the incidence of breast cancer by 49 percent as compared with the incidence with placebo. Although two European randomized, controlled trials of tamoxifen did not show a benefit, these trials were statistically underpowered, had high rates of noncompliance, and included women who continued to take hormone-replacement therapy.[31,32] Tamoxifen is currently the only drug approved by the Food and Drug Administration for reducing the risk of breast cancer. Because published trials of raloxifene were not designed to assess its efficacy in preventing breast cancer, raloxifene has not been approved for reducing the risk of breast cancer.[33] Clinical trials are now comparing the efficacy of raloxifene with that of tamoxifen in reducing the risk of breast cancer.

Assessment of breast-cancer risk is important in making decisions about tamoxifen, for several reasons. First, because the Breast Cancer Prevention Trial enrolled only women with a five-year breast-cancer risk of 1.7 percent or more, it is unclear whether the benefit of tamoxifen applies to women at lower risk. Clinical experts in breast-cancer prevention recommend that tamoxifen be used only by women whose risk of breast cancer is at or above this threshold.[33]

Second, although they are rare, tamoxifen has side effects, including venous thromboembolism, endometrial cancer, and cataracts. In women taking tamoxifen, deep venous thromboses occurred 1.6 times as often and pulmonary emboli 3 times as often as in control women. The increased risk of endometrial cancer was also substantial (relative risk, 2.5); however, the increased risk was restricted to early-stage cancers in postmenopausal women. Cataract surgery was required almost twice as often among women taking tamoxifen. Thus, for women to choose or for physicians to advocate the preventive use of tamoxifen, the benefits must outweigh these risks. Although no formal risk–benefit analysis is currently available, the higher a woman's risk of breast cancer, the more likely it is that the reduction in the incidence of breast cancer will outweigh these other risks.

Third, as the risk of breast cancer increases, the absolute benefit of tamoxifen increases. For women at relatively low risk of breast cancer, the absolute benefit may be relatively small. For women at very high risk of breast cancer, the absolute benefit is correspondingly great.

### Decisions about Prophylactic Mastectomy

A recent retrospective cohort analysis of 639 women at high risk for breast cancer found that prophylactic mastectomy reduced the risk by more than 90 percent.[34] Although this risk reduction is impressive,

the trade-offs involved in prophylactic mastectomy are substantial. Prophylactic mastectomy involves extensive and potentially disfiguring surgery with unknown effects on the long-term quality of life.[35] Furthermore, the reduction in breast-cancer risk achieved by prophylactic mastectomy depends on a woman's underlying risk of breast cancer. A decision analysis involving women who were carriers of *BRCA1* or *BRCA2* mutations found that the benefit of prophylactic mastectomy differed substantially according to the breast-cancer risk conferred by the mutations.[36] For women with an estimated lifetime risk of 40 percent (approximately four times the population risk), prophylactic mastectomy would add almost three years of life, whereas for women with an estimated lifetime risk of 85 percent, prophylactic mastectomy would add more than five years.

## HOW TO EVALUATE BREAST-CANCER RISK

### Average Risk

Understanding the average risk of breast cancer provides a necessary context for individual risk assessments. The average lifetime risk of breast cancer in the U.S. female population at birth is 12 percent, or approximately one in eight.[37] The longer a woman lives without cancer, the lower is her risk of breast cancer over the remainder of her lifetime. Thus, a 50-year-old woman who has not had breast cancer has an 11 percent chance of having breast cancer in her lifetime, and a 70-year-old woman who has not had breast cancer has a 7 percent chance of having breast cancer in her lifetime.

### Epidemiologic Risk Factors

Many studies have evaluated risk factors for breast cancer.[13-15,38-46] Several factors have been consistently associated with an increased risk (Table 1). However, because many of these risk factors may interact, evaluating the risk conferred by combinations of risk factors is challenging. Other risk factors have been less consistently associated with breast cancer (such as diet, use of oral contraceptives, lactation, and abortion) or are rare in the general population (such as radiation exposure), and are not included in currently used prediction models.[41-46]

### Risk-Prediction Models

Four models are currently available to predict the risk of breast cancer, of which two are used most often. The most commonly used model was developed by Gail et al. from the Breast Cancer Detection Demonstration Project, a large mammographic-screening program conducted in the 1970s.[39] This model incorporates the number of first-degree relatives with breast cancer (0, 1, or ≥2), age at menarche (<12, 12 to 13, or ≥14 years), age at first live birth (<20, 20 to 24, 25 to 29 or nulliparous, or ≥30 years), and the number of breast biopsies (0, 1, or ≥2). It predicts the cumulative risk of breast cancer according to decade up to the age of 90 years. To determine eligibility for trial entry, the Breast Cancer Prevention Trial used a revised Gail model that also incorporates race, presence of atypical hyperplasia on breast biopsy, and 1987 population rates of breast cancer and death from other causes.

To calculate breast-cancer risk with the Gail model, a woman's risk factors are translated into an overall risk score by multiplying her relative risks from several categories (age at menarche, number of breast biopsies, family history, and age at first live birth) (Table 2). This risk score is then multiplied by an adjusted population risk of breast cancer to determine the individual risk of breast cancer. Because the effects of risk factors interact and vary with age, the risk of breast cancer is most easily calculated with a software program that is available from the National Cancer Institute at http://cancernet.nci.nih.gov/h_detect.html. The results of calculations of five-year and lifetime risks of breast cancer with the Gail model for women with various risk factors are presented in Table 3.

The other commonly used prediction model was developed by Claus et al. on the basis of data from the Cancer and Steroid Hormone Study, a large, population-based, case–control study of breast cancer.[47] This model is based on assumptions of the prevalence of high-penetrance genes for susceptibility to breast cancer. As compared with the Gail model, the Claus model incorporates more extensive information about

**TABLE 1.** ESTABLISHED RISK FACTORS FOR BREAST CANCER.

| RISK FACTOR | RELATIVE RISK | STUDY |
|---|---|---|
| Age (≥50 vs. <50 yr) | 6.5 | Ries et al.[1] |
| Family history of breast cancer | | |
| First-degree relative | 1.4–13.6 | Rockhill et al.[13]<br>Madigan et al.[14]<br>Bruzzi et al.[15]<br>Slattery and Kerber[38]<br>Gail et al.[39] |
| Second-degree relative | 1.5–1.8 | Slattery and Kerber[38] |
| Age at menarche (<12 vs. ≥14 yr) | 1.2–1.5 | Rockhill et al.[13]<br>Bruzzi et al.[15]<br>Gail et al.[39] |
| Age at menopause (≥55 vs. <55 yr) | 1.5–2.0 | Madigan et al.[14]<br>Bruzzi et al.[15] |
| Age at first live birth (>30 vs. <20 yr) | 1.3–2.2 | Rockhill et al.[13]<br>Madigan et al.[14]<br>Bruzzi et al.[15]<br>Gail et al.[39] |
| Benign breast disease | | |
| Breast biopsy (any histologic finding) | 1.5–1.8 | Rockhill et al.[13]<br>Bruzzi et al.[15]<br>Gail et al.[39] |
| Atypical hyperplasia | 4.0–4.4 | Dupont and Page[40] |
| Hormone-replacement therapy | 1.0–1.5 | Folsom et al.[6]<br>Colditz et al.[7] |

**TABLE 2.** RELATIVE RISK OF BREAST CANCER ACCORDING TO THE GAIL MODEL.*

| RISK FACTOR | RELATIVE RISK |
|---|---|
| **Category A** | |
| Age at menarche | |
| ≥14 yr | 1.00 |
| 12–13 yr | 1.10 |
| <12 yr | 1.21 |
| **Category B** | |
| No. of breast biopsies and woman's age | |
| 0 | |
| Any age | 1.00 |
| 1 | |
| <50 yr | 1.70 |
| ≥50 yr | 1.27 |
| ≥2 | |
| <50 yr | 2.88 |
| ≥50 yr | 1.62 |
| **Category C** | |
| No. of 1st-degree relatives with breast cancer and woman's age at 1st live birth | |
| 0 | |
| <20 yr | 1.00 |
| 20–24 yr | 1.24 |
| 25–29 yr or nulliparous | 1.55 |
| ≥30 yr | 1.93 |
| 1 | |
| <20 yr | 2.61 |
| 20–24 yr | 2.68 |
| 25–29 yr or nulliparous | 2.76 |
| ≥30 yr | 2.83 |
| ≥2 | |
| <20 yr | 6.80 |
| 20–24 yr | 5.78 |
| 25–29 yr or nulliparous | 4.91 |
| ≥30 yr | 4.17 |

*Composite risk scores for women under 50 years of age and for those 50 or more years old are derived by multiplying the appropriate relative risks from categories A, B, and C. These risk scores are then translated into five-year and lifetime risks by using adjusted population rates of breast cancer.

family history, but it excludes risk factors other than family history. On the basis of knowledge of first- and second-degree relatives with breast cancer and their age at diagnosis, the Claus model provides individual estimates of breast-cancer risk according to decade from 29 to 79 years of age. Claus-model predictions for women with one first-degree relative with breast cancer, one second-degree relative with breast cancer, and two first-degree relatives with breast cancer are shown in Table 4. Predictions for other combinations of relatives with breast cancer (two second-degree relatives, mother and maternal aunt, and mother and paternal aunt) are also available.[47]

Two other risk-prediction models were developed for genetic counseling of women with a strong family history of breast cancer.[48,49] These models apply only to women who have either a mother or a sister with breast cancer and are less commonly used than the Gail and Claus models.

Although relatively few studies have attempted to validate risk-prediction models for breast cancer, the Gail model has received the most attention, with validation studies in four populations.[50-53] In general, the Gail model appears to be accurate for women undergoing routine mammographic screening but probably overestimates the risk among young women who are not undergoing regular mammography. An analysis of the Breast Cancer Prevention Trial data found that the ratio of observed to predicted cancers among the study participants was 1.03 (95 percent confidence interval, 0.88 to 1.21).[51] The one study that compared the Gail and Claus models found only moderate agreement between the two methods in a high-risk population of women (intraclass correlation coefficients, 0.43 to 0.55).[54] Thus, for women to whom the Claus model is applicable (those with at least one first- or second-degree relative with breast

**TABLE 3.** CLINICAL EXAMPLES OF RISK PREDICTIONS ACCORDING TO THE GAIL MODEL.

| CURRENT AGE (YR) | RACE | NO. OF FIRST-DEGREE RELATIVES WITH BREAST CANCER | NO. OF BREAST BIOPSIES | AGE AT MENARCHE | AGE AT FIRST LIVE BIRTH | 5-YEAR BREAST-CANCER RISK | BREAST-CANCER RISK TO THE AGE OF 90 |
|---|---|---|---|---|---|---|---|
| | | | | years | | percent | |
| 40 | Black | 0 | 0 | 14 | 19 | 0.3 | 3.7 |
| 40 | White | 0 | 0 | 14 | 19 | 0.4 | 6.7 |
| 40 | White | 1 | 0 | 14 | 19 | 0.9 | 16.4 |
| 40 | White | 1 | 1 | 14 | 19 | 1.5 | 19.9 |
| 40 | White | 1 | 1 | 12 | 19 | 1.6 | 21.6 |
| 40 | White | 1 | 1 | 12 | 30 | 1.8 | 23.2 |
| 40 | White | 2 | 2 | 12 | 30 | 3.4 | 25.2 |
| 50 | White | 1 | 1 | 12 | 30 | 2.3 | 20.1 |
| 60 | Black | 1 | 1 | 12 | 30 | 2.0 | 9.4 |
| 60 | White | 1 | 1 | 12 | 30 | 3.4 | 16.6 |

**TABLE 4.** CUMULATIVE RISK OF BREAST CANCER ACCORDING TO THE CLAUS MODEL.

| NO. OF RELATIVES WITH BREAST CANCER AND THEIR AGE AT DIAGNOSIS | CUMULATIVE BREAST-CANCER RISK ACCORDING TO AGE | | | | |
|---|---|---|---|---|---|
| | 39 YR | 49 YR | 59 YR | 69 YR | 79 YR |
| | | | percent | | |
| **One 1st-degree relative** | | | | | |
| 20–29 yr | 2.5 | 6.2 | 11.6 | 17.1 | 21.1 |
| 30–39 yr | 1.7 | 4.4 | 8.6 | 13.0 | 16.5 |
| 40–49 yr | 1.2 | 3.2 | 6.4 | 10.1 | 13.2 |
| 50–59 yr | 0.8 | 2.3 | 4.9 | 8.2 | 11.0 |
| 60–69 yr | 0.6 | 1.8 | 4.0 | 7.0 | 9.6 |
| 70–79 yr | 0.5 | 1.5 | 3.5 | 6.2 | 8.8 |
| **One 2nd-degree relative** | | | | | |
| 20–29 yr | 1.4 | 3.5 | 7.0 | 11.0 | 14.2 |
| 30–39 yr | 1.0 | 2.7 | 5.6 | 9.0 | 12.0 |
| 40–49 yr | 0.7 | 2.1 | 4.5 | 7.6 | 10.4 |
| 50–59 yr | 0.6 | 1.7 | 3.8 | 6.7 | 9.4 |
| 60–69 yr | 0.5 | 1.7 | 3.8 | 6.7 | 9.4 |
| 70–79 yr | 0.4 | 1.3 | 3.2 | 5.8 | 8.3 |
| **Two 1st-degree relatives** | | | | | |
| Younger age at diagnosis 20–29 yr | | | | | |
| Older age at diagnosis | | | | | |
| 20–29 yr | 6.9 | 16.6 | 29.5 | 41.2 | 48.4 |
| 30–39 yr | 6.6 | 15.7 | 27.9 | 39.1 | 46.0 |
| 40–49 yr | 6.1 | 14.6 | 26.1 | 36.6 | 43.4 |
| 50–59 yr | 5.5 | 13.3 | 23.8 | 33.5 | 39.7 |
| 60–69 yr | 4.8 | 11.7 | 21.0 | 29.7 | 35.4 |
| 70–79 yr | 4.1 | 9.9 | 17.9 | 25.6 | 30.8 |
| Younger age at diagnosis 30–39 yr | | | | | |
| Older age at diagnosis | | | | | |
| 30–39 yr | 6.2 | 14.8 | 26.5 | 37.1 | 43.7 |
| 40–49 yr | 5.6 | 13.4 | 23.9 | 33.7 | 39.9 |
| 50–59 yr | 4.8 | 11.6 | 20.9 | 29.6 | 35.3 |
| 60–69 yr | 4.0 | 9.6 | 17.5 | 25.1 | 30.2 |
| 70–79 yr | 3.2 | 7.7 | 14.3 | 20.7 | 25.2 |
| Younger age at diagnosis 40–49 yr | | | | | |
| Older age at diagnosis | | | | | |
| 40–49 yr | 4.8 | 11.7 | 21.0 | 29.8 | 35.4 |
| 50–59 yr | 3.9 | 9.6 | 17.4 | 24.9 | 30.0 |
| 60–69 yr | 3.0 | 7.5 | 13.9 | 20.2 | 24.6 |
| 70–79 yr | 2.3 | 5.8 | 10.8 | 16.1 | 20.0 |
| Younger age at diagnosis 50–59 yr | | | | | |
| Older age at diagnosis | | | | | |
| 50–59 yr | 3.0 | 7.5 | 13.8 | 20.0 | 24.5 |
| 60–69 yr | 2.2 | 5.6 | 10.5 | 15.7 | 19.5 |
| 70–79 yr | 1.6 | 4.2 | 8.1 | 12.4 | 15.8 |
| Younger age at diagnosis 60–69 yr | | | | | |
| Older age at diagnosis | | | | | |
| 60–69 yr | 1.6 | 4.1 | 8.0 | 12.2 | 15.6 |
| 70–79 yr | 1.2 | 3.0 | 6.1 | 9.8 | 12.8 |
| Younger age at diagnosis 70–79 yr | | | | | |
| Older age at diagnosis | | | | | |
| 70–79 yr | 0.8 | 2.3 | 4.9 | 8.1 | 10.9 |

cancer), the predictions of the Gail and Claus models may differ.

### Genetic-Susceptibility Testing

Two major breast-cancer-susceptibility genes have been identified, *BRCA1* and *BRCA2*.[55,56] Women with mutations in either of these genes have a lifetime risk of breast cancer of 60 to 85 percent and a lifetime risk of ovarian cancer of 15 to 40 percent.[57,58] Several studies have identified familial characteristics that increase the likelihood of carrying a *BRCA1* or *BRCA2* mutation.[59,60] These include early-onset breast cancer, breast and ovarian cancer, and Ashkenazi Jewish ancestry.

Testing for mutations in *BRCA1* and *BRCA2* is an important tool for predicting breast-cancer risk in two sets of circumstances.[61] First, in families with known mutations in *BRCA1* or *BRCA2*, genetic testing can separate women who carry the familial mutation (with the associated 60 to 85 percent lifetime risk of breast cancer) from those who do not. Women who test negative are at the same risk as women without a family

history of breast cancer. Second, in families that have risk factors for carrying a *BRCA* mutation but do not have a known mutation, genetic testing can identify a substantial number of women with *BRCA* mutations. These women also have a lifetime breast-cancer risk of 60 to 85 percent. However, women from these families who test negative for *BRCA* mutations remain at increased risk because of their family history of breast cancer. Although their risk falls by an amount equal to the probability that *BRCA* mutations would have explained their particular familial pattern, this decrement is often relatively small, except in the Ashkenazi population, where *BRCA* mutations may explain a substantial proportion of hereditary breast cancer. Models are not currently available to adjust predictions of breast-cancer risk for a negative *BRCA* test.

Although the probability of carrying a *BRCA1* or *BRCA2* mutation varies substantially according to the actual combination of risk factors in a given family, the presence of certain major risk factors or combinations of risk factors has been proposed as a reasonable criterion for consideration of testing for *BRCA* mutations (Table 5). As a first step in this process, the patient is given genetic counseling before testing to provide her with information about the probability that she carries a mutation in *BRCA1* or *BRCA2* and the benefits, risks, and limitations of testing. This is complex information that a woman needs to make an informed decision about *BRCA* testing.[61]

For women from families without risk factors for a *BRCA* mutation, genetic testing is unlikely to provide useful information about breast-cancer risk. Because *BRCA* mutations are rare in the non-Ashkenazi general population, with an estimated prevalence of approximately 1 in 1000, they account for less than 5 percent of the overall population burden of breast cancer.[62] Thus, women from low-risk families rarely test positive, and a negative test will not provide important new information about their risk of breast cancer.

#### Selecting a Prediction Method

Several factors influence the selection of a risk-prediction method for an individual woman. Different methods may be appropriate in different settings. Although qualitative assessment of breast-cancer risk factors may be sufficient for a woman 40 to 49 years old to make a decision about mammography, determining eligibility for tamoxifen prophylaxis requires a numerical probability estimate from a prediction model, and deciding whether to undergo prophylactic mastectomy often involves genetic-susceptibility testing. Although many women have difficulty manipulating probabilities in numerical exercises, genetic counseling and programs for the assessment of cancer risk have traditionally used probabilistic information in counseling.[63,64] In most settings, a numerical estimate of a woman's risk is useful information that can also be presented qualitatively.

**TABLE 5.** FAMILY-HISTORY RISK FACTORS FOR CARRYING A *BRCA1* OR *BRCA2* MUTATION.

| |
|---|
| Known *BRCA1* or *BRCA2* mutation |
| Breast and ovarian cancer |
| Two or more family members under 50 years of age with breast cancer |
| Male breast cancer |
| One or more family members under 50 with breast cancer plus Ashkenazi ancestry |
| Ovarian cancer plus Ashkenazi ancestry |

For a woman with risk factors for carrying a *BRCA1* or *BRCA2* mutation, the first step is to determine whether she is interested in pursuing genetic testing. If she is, she should be referred, if possible, to a center that provides specialized genetic counseling for *BRCA* testing. A list of specialized centers can be found at http://cancernet.nci.nih.gov/genesrch.shtml or can be obtained by telephoning the Cancer Information Service at 1-800-422-6237 (1-800-4-CANCER). If referral is not possible or desired, appropriate individual counseling about the potential benefits, risks, and limitations of testing should be provided by the health care professional who ordered the test.[61] For women who choose to undergo testing and are found to carry a *BRCA* mutation, current evidence suggests that the lifetime risk of breast cancer is between 60 and 85 percent, and further assessment of breast-cancer risk with other prediction models is not meaningful.

For women with risk factors for carrying a *BRCA1* or *BRCA2* mutation who test negative for *BRCA* mutations or who choose not to undergo testing, and for women with one or more first- or second-degree relatives with breast cancer, the Claus model offers the most comprehensive assessment of family history. It can be supplemented by the Gail model, as modified by the Breast Cancer Prevention Trial, for purposes of making decisions about tamoxifen use. For women without first- or second-degree relatives with breast cancer, the Claus model is not applicable.

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Appendix I:

"Beliefs about breast cancer risk and use of post menopausal hormone replacement therapy"

# BELIEFS ABOUT BREAST CANCER RISK AND USE OF POSTMENOPAUSAL HORMONE REPLACEMENT THERAPY

KATRINA ARMSTRONG, MD, MSCE, SHARON POPIK, MD,
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# Beliefs about Breast Cancer Risk and Use of Postmenopausal Hormone Replacement Therapy

KATRINA ARMSTRONG, MD, MSCE, SHARON POPIK, MD, CARMEN GUERRA, MD, PETER A. UBEL, MD

*Background.* Postmenopausal hormone replacement therapy (HRT) decreases the risks of coronary heart disease and osteoporosis, but increases the risk of breast cancer. Although only 20–30% of postmenopausal women in the United States take HRT, the relationship between breast cancer risk perception and use of HRT is not known. *Objective.* To assess the impact of belief that HRT increases breast cancer risk and high perceived risk of breast cancer on the use of HRT. *Design.* Cross-sectional mailed survey. *Participants.* 189 randomly selected postmenopausal women from a general internal medicine practice in the Philadelphia area. *Main results.* Of the 268 women (67%) who returned surveys, 189 were postmenopausal; 70 (37%) were currently using HRT and 21 (11%) had previously used HRT. Respondents' mean age was 59.6 years; 64% were Caucasian, and 33% had completed college. Fifty-nine women (33%) thought HRT increased the risk of breast cancer, 22 (12%) thought it did not, and 100 (55%) were unsure. Mean perceived lifetime risk of breast cancer was 31% (range 0%–100%). After multivariate adjustment, current use of HRT was inversely associated with age (OR 0.96 for each one-year increase, 95% CI 0.94–0.98), and positively associated with Caucasian race (OR 2.73, 95% CI 1.40–5.32). Use of HRT was not associated with belief that HRT increases the risk of breast cancer, breast cancer risk perception, or perceived severity of breast cancer. *Conclusions.* Belief that HRT increases the risk of breast cancer and high perceptions of breast cancer risk may not be important barriers to use of HRT. Efforts to improve decision making about HRT should focus on previously established barriers, such as perceptions of menopause and lack of physician discussion, rather than misconceptions about breast cancer risk. *Key words*: postmenopausal hormone replacement therapy; breast cancer risk perception. **(Med Decis Making 2000;20:308–313)**

Observational studies suggest that long-term postmenopausal hormone replacement therapy (HRT) reduces the risks of coronary heart disease (CHD) and osteoporosis, but increases the risk of breast cancer.[1–4] Decision and cost–effectiveness analyses have confirmed that the average woman will gain life expectancy with the use of HRT.[5–7] Despite this evidence, only 50–60% of women begin HRT at the time of menopause and only 20–30% of women are still taking HRT five years after the onset of menopause.[8–10]

Several prior studies have examined factors associated with the use of HRT. Use of HRT is greater among women who have undergone hysterectomy, have completed college, have discussed HRT with their physician, see a gynecologist, are Caucasian, believe that menopause is a medical condition that should be treated, or believe that reduced estrogen levels lead to osteoporosis.[9–18] Established barriers to the use of HRT include side effects (primarily vaginal bleeding) and a general belief HRT might be harmful.

Although review articles and the lay press frequently identify fear of breast cancer as a barrier to use of HRT, to our knowledge no published study has examined the relationship between belief that HRT increases the risk of breast cancer and the use of HRT or between perceived risk of breast cancer and the use of HRT.[19–23] One survey of pre- and postmenopausal women found that 65% of the women

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rated their risks of breast cancer as more important than their risks of heart disease, but the relationship between these perceptions and HRT use was not evaluated.[17] Another study found that four of 27 women who did not begin HRT gave concern over breast cancer as a reason for refusal, but concerns about breast cancer were not assessed among women who were using HRT.[18] Thus, the aims of our study were: 1) to evaluate the relationship between belief that HRT increases the risk of breast cancer and use of HRT; 2) to evaluate the relationship between the perceived risk of breast cancer and use of HRT; and 3) to identify other factors influencing use of HRT in a general internal medicine patient population.

## Methods

### STUDY DESIGN

A cross-sectional mailed survey was used to measure use of HRT, belief that HRT increases the risk of breast cancer, breast cancer risk perception, and other factors that might predict use of HRT using the framework of the health belief model (figure 1). The study protocol was approved by the Institutional Review Board of the University of Pennsylvania.

### SUBJECT SELECTION

From the 7,296 women 18 years of age or older seen at a University of Pennsylvania faculty general internal medicine practice between November 1996 and August 1997, 400 women were randomly selected by computer. Women who were premenopausal or had a diagnosis of breast cancer were excluded at the time the questionnaire was returned.

### INSTRUMENT DEVELOPMENT

A questionnaire was developed to measure: 1) current and former use of HRT; 2) menopausal status; 3) belief that HRT increases the risk of breast cancer; 4) breast cancer risk perception; 5) perceived severity of breast cancer; 6) belief that HRT decreases the risk of coronary heart disease (CHD); 7) perceived risk and severity of CHD and osteoporotic fracture; and 8) sociodemographic characteristics, including age, race, religion, education, and marital status. Belief that HRT increases the risk of breast cancer was measured by asking: "Do you think taking hormone replacement therapy after menopause increases your chance of developing breast cancer?" Because there is no established and validated single measure of perceived breast cancer risk and prior studies using different measures have found different results,

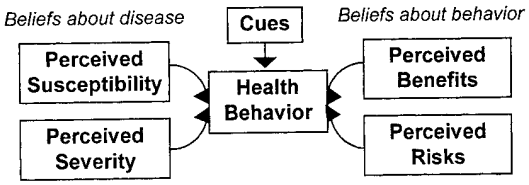


FIGURE 1. Health belief model.

perceived risk of breast cancer was measured with three items: 1) "What do you think the chance is you will develop breast cancer in your lifetime? *Please pick a number between 0% and 100%*"; 2) "How would you rate your chance of developing breast cancer?" This question had a five-point Likert response scale from very low to very high; 3) "What do you think the chance you will get breast cancer in your lifetime is compared to the chance the average woman will get breast cancer in her lifetime?" This question had a five-point Likert response scale from much lower to much higher. Perceived risks of CHD and osteoporosis were measured with single items asking for a numeric estimate between 0% and 100% of the lifetime risk of heart attack or breaking a bone because of osteoporosis. Perceived severity was measured by asking "How serious a health problem do you think (breast cancer, heart attack or breaking a bone because of osteoporosis) is?" This question had a five-point Likert response scale from extremely serious to not at all serious.

### STATISTICAL ANALYSIS

All data collected were analyzed using descriptive statistics. Our primary analysis compared women currently using HRT with women who had never used HRT using independent sample t-tests for continuous variables and ordinary chi-square tests for categorical variables. Numeric perceived breast cancer risk was examined both as a continuous variable (0% to 100%) and as a categorical variable (< 10%, 10–50%, and > 50%). Wilcoxon rank-sum test was used for confirmation of analyses using Likert-scaled variables. Multiple logistic regression adjusted the association between use of HRT and family history of breast cancer for potential confounding. Variables that were associated with use of HRT were added to the regression model sequentially and tested using likelihood-ratio statistics. Age was also examined as a categorical variable (< 60, 60–69, > 69 years). Interaction terms were tested for the interaction of perceived risk and perceived severity of breast cancer and belief about the effect of HRT on breast cancer risk and family history of breast cancer. Secondary analyses were conducted for the comparison of ever (current +prior)

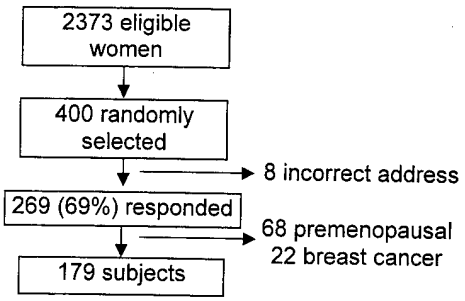


FIGURE 2. Subject selection and response.

users vs never users. All p values are two-sided. A sample size of 400 women provided 80% power to detect a difference of 10% in breast cancer risk perception between women who did and did not use HRT with a type I error of 0.05, assuming a response rate of 70%, that two thirds of women were postmenopausal, and a standard deviation of breast cancer risk perception of 20%.

## Results

From the 400 surveys mailed, 179 eligible women completed surveys (figure 2). Sixty-seven women (37%) were currently taking HRT, 19 (11%) had previously taken HRT, and 93 (52%) had never taken HRT. Characteristics of these three groups are reported in table 1.

Among all respondents, only a third of the women (33%) thought HRT increased the risk of breast cancer. Mean perceived lifetime risk of breast cancer was 31% (range 0 to 100%). Ninety-three women (54%) rated breast cancer risk as moderately low or very low, while 21 (12%) rated it as moderately high or very high. Eighty women (44%) thought their risk was lower than the average woman's, while only 24 (13%) thought it was higher. Measures of perceived breast cancer risk were correlated (Pearson's correlation coefficients 0.64–0.74, p values $< 0.0005$).

Current HRT use was not associated with belief that HRT increases the risk of breast cancer or any measure of perceived risk of breast cancer (p values $> 0.27$) (figure 3). In fact, numeric perceived risk of breast cancer was slightly higher among women who currently used HRT than among women who did not. However, perceived risk was measured simultaneously with use of HRT and, thus, may have been affected by HRT use. Categorizing numeric perceived breast cancer risk as low, medium, and high ($< 10\%$, 10–49%, $> 49\%$) did not lead to an association with use of HRT. Current HRT use was not associated with perceived risk of heart attack or osteoporotic fracture, perceived severity of breast cancer, heart attack, or osteoporotic fracture, belief that HRT decreases the risk of CHD, or family history of breast cancer. Furthermore, there was no interaction between perceived risk and perceived severity of breast cancer or between family history of breast cancer and belief about HRT's effect on breast cancer risk.

Current HRT use was inversely associated with increasing age and with African American race and positively associated with being married. After mul-

**Table 1** • Characteristics of Current, Prior, and Never Users of HRT

| | Current Use ($n = 67$) | Prior Use ($n = 19$) | Never Use ($n = 93$) | p Value |
|---|---|---|---|---|
| Sociodemographics | | | | |
| Age (mean +/−SD) | 55.5 years +/− 11.4 | 53.7 years +/− 9.5 | 54.0 years +/− 15.8 | 0.001 |
| African American | 18.2% | 26.3% | 33.0% | 0.04 |
| Married | 55.2% | 47.4% | 39.8% | 0.05 |
| College education | 37.3% | 26.3% | 32.2% | 0.51 |
| Family history of breast CA | 32.3% | 21.1% | 27.2% | 0.49 |
| Risk and benefit of HRT | | | | |
| HRT ↑ risk of breast CA | 36.5% | 26.3% | 33.0% | 0.67 |
| HRT ↓ risk of heart attack | 39.7% | 36.8% | 41.3% | 0.78 |
| Perceived risk,* mean (SD) | | | | |
| Breast CA | 34.6 (23.8) | 32.3 (31.2) | 28.0 (22.4) | 0.27 |
| Heart attack | 39.5 (26.9) | 31.8 (22.1) | 39.1 (25.5) | 0.67 |
| Osteoporotic fracture | 28.4 (22.9) | 36.1 (24.8) | 30.7 (26.9) | 0.56 |
| Perceived Severity | | | | |
| Breast CA | 61.2 | 68.4 | 73.6 | 0.10 |
| Heart attack | 72.7 | 73.6 | 71.7 | 0.82 |
| Osteoporotic fracture | 22.7 | 26.3 | 21.1 | 0.65 |

*Numeric estimate of lifetime risk between 0 and 100%.

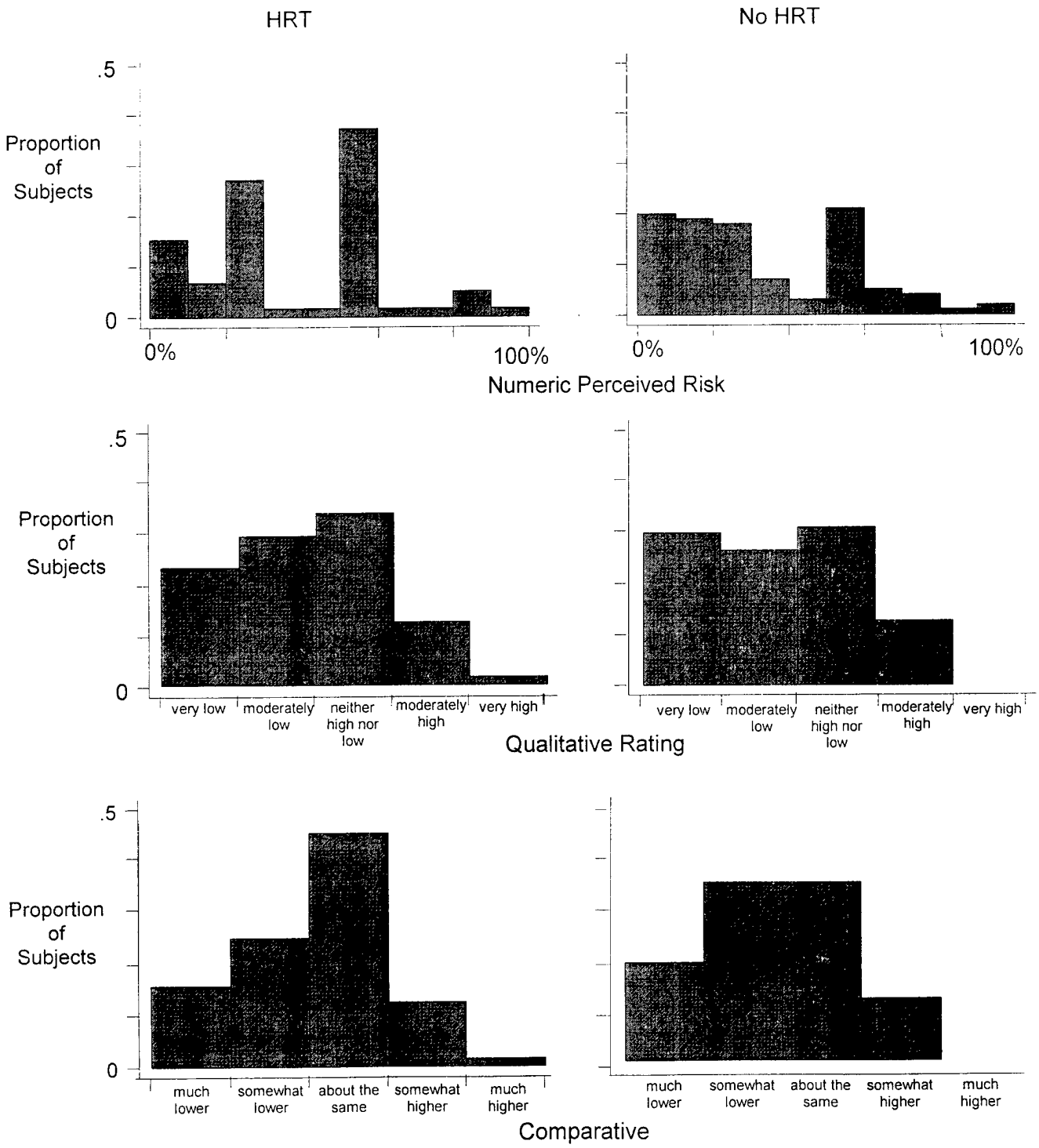


FIGURE 3. Perceived breast cancer risk according to current use of HRT.

tivariable adjustment, current HRT use remained associated with African American race (OR 0.39, 95% CI 0.17–0.89) and increasing age (OR 0.93 for one-year increase, 95% CI 0.89–0.96), but not with marital status. These analyses did not differ significantly when comparing ever users (current + prior user) with never users.

## Discussion

Few medical decisions have received more attention from physicians or patients than postmenopausal HRT. Although many experts advocate HRT because of the potential public health impact of the reduction in CHD risk, individual decisions about

HRT are difficult because of the many competing risks and benefits of HRT, the considerable epidemiologic uncertainty about the outcomes of HRT, and the potential emotional issues surrounding menopause. Understanding the factors that influence this complex decision is an important step towards improving informed decision making for all women considering HRT.

To our knowledge, this is the first study that suggests that belief that HRT increases the risk of breast cancer and perceived risk of breast cancer may not affect decisions about HRT. Despite widespread media attention to breast cancer, this empirically based observation suggests that fear of breast cancer may not be an important barrier to use of HRT for many postmenopausal women.

Although the simplest explanation for the observed lack of association is that perceptions about breast cancer and the effect of HRT on breast cancer do not influence use of HRT for most women, it is important to consider several other potential explanations. First, the decision about HRT may be so complex and involve so many factors that these perceptions may play relatively small roles, which were unable to be captured in a study of this size. Although we could have missed a difference in risk perception less than the 10% our study was powered to detect, our point estimate actually suggested that women with a higher perceived breast cancer risk were more likely to take HRT—although, again, this relationship may be altered if taking HRT affects breast cancer risk perception. Second, difficulties in measurement of true beliefs and risk perceptions may have made it more difficult to find associations. We measured beliefs about the effect of HRT on breast cancer risk with a single item and were not able to examine variations of this relationship, such as the effects of alternative durations of HRT use. Although we used three commonly used measures of breast cancer risk perception, these measures may not have accurately represented true risk perception. Third, we asked only about perceptions of the effect of HRT on breast cancer, breast cancer risk, and breast cancer severity. Other factors such as breast cancer worry or anxiety may be more important in the decision about HRT.

Our finding that HRT is less commonly used by African American women is supported by several previous studies.[8,9,11] Two studies investigating this discrepancy have found that African American women were less likely to have been recommended HRT by their physicians and had more positive attitudes but less knowledge about menopause.[24,25]

While our study confirms other reports that found most women overestimate their numeric personal risks of breast cancer, over half of the women in our study rated their risks as moderately or very low, and over half felt their risks were lower than that of the average woman. Our finding that women see their risks of developing breast cancer as lower than that of the average woman even when they substantially overestimate the true probability confirms a recent published study of alternative measures of breast cancer risk and suggests that numeric overestimation may be more accurately attributed to difficulty in estimating and using probabilities than true overestimation of breast cancer risk.[26,27]

Our study had several limitations. As we had a low (although still acceptable) response rate, respondents may have differed from non-respondents. However, it is unlikely that any response bias could have obscured a strong association between perceived breast cancer risk and use of HRT. We used self-report to measure use of HRT and may have misclassified some respondents according to HRT use. While such misclassification may have made it slightly more difficult to find an association, self-report has been used and validated in many studies, and the degree of misclassification is likely to have been small. We measured breast cancer risk perception and use of HRT simultaneously; thus, it is possible use of HRT influenced risk perception. However, because only a third of the women believed HRT increased the risk of breast cancer and neither use of HRT nor breast cancer risk perception was associated with this belief, it is possible that use of HRT did not substantively raise perceptions of breast cancer risk. We did not have data about how long the women intended to use HRT, and fears of breast cancer may be a stronger deterrent to women intending to take long-term HRT. We surveyed patients from a single practice—further work is needed to determine the generalizability of our results.

Use of HRT is a complex, difficult decision involving many benefits, risks, and tradeoffs. Despite widespread media attention to breast cancer, our study suggests that women are not deciding against HRT because of fear of the effect of HRT on breast cancer risk or high perceptions of breast cancer risk. Although further research is needed to better understand decisions about HRT, current efforts to improve decision making about HRT should focus on previously established barriers, such as perceptions of menopause and lack of physician discussion, rather than misconceptions about breast cancer risk.

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Appendix J:
"Factors associated with decisions about clinical BRCA1/2 testing"

# Factors Associated with Decisions about Clinical *BRCA1/2* Testing

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## ABSTRACT

**BACKGROUND:** Testing for mutations in *BRCA1* and *BRCA2* can provide important information about breast and ovarian cancer risk to a small but identifiable subgroup of women. Women who test positive for a *BRCA1/2* mutation can pursue more aggressive cancer surveillance and prevention regimens. Among families with known mutations, women who test negative may avoid unnecessary interventions. Currently little is known about the factors associated with use of clinical *BRCA1/2* testing.

**OBJECTIVE:** To determine the factors associated with decisions about clinical *BRCA1/2* testing among women undergoing clinical *BRCA1/2* counseling.

**DESIGN:** Retrospective cohort study of women who participated in a university based clinic offering breast cancer risk assessment, genetic counseling and *BRCA1/2* testing between January 1996 and April 1998.

**RESULTS:** From the 251 eligible women who responded to a follow-up survey, 125 (50%) had undergone or were undergoing testing, 86 (34%) had decided not to undergo *BRCA1/2* testing, and 40 (16%) had not decided about testing. After multivariate adjustment, women who chose to undergo *BRCA1/2* testing were more likely to have a known familial mutation (OR 7.46, 95% CI 0.97-62.16), more likely to be Ashkenazi Jewish (OR 6.37, 95% CI 2.68-15.12), more likely to want cancer risk information for family members (OR 1.93, 95% CI 0.99-4.14),more likely to want information about ovarian cancer risk (OR 1.69, 95% CI 1.18-3.69), and less likely to be concerned about insurance or job discrimination (OR 0.45, 95% CI 0.21-0.94). These associations were also found in the subgroup of women with a predicted probability of a *BRCA1* mutation $\geq 5\%$.

**CONCLUSIONS:** Our study suggests that approximately half of eligible women choose to undergo clinical *BRCA1/2* testing after participating in counseling. Women who have the highest risk of carrying a mutation, and thus the greatest probability of gaining some useful information from the test results, are most likely to undergo testing. Women who undergo testing are also more interested in ovarian cancer risk information and less concerned about job and insurance discrimination.

## INTRODUCTION

Mutations in the cancer susceptibility genes *BRCA1* and *BRCA2* are associated with a significantly increased lifetime risk of breast and ovarian cancer. [1,2] Although interest in genetic testing for cancer susceptibility has grown quickly in the medical community, deciding about *BRCA1/2* testing remains potentially a complex and difficult process.

The primary benefit of *BRCA1/2* testing is the information that can be gained about individual and familial breast and ovarian cancer risk. This information may have significant implications for decisions about cancer surveillance and cancer prevention.[3,4] The limitations and risks of *BRCA1/2* testing are complex. [4-6] Currently available options for cancer surveillance and prevention have limited efficacy and/or involve significant trade-offs. [4] Furthermore, the cancer risk information gained from testing is limited in most contexts. Outside of families with known mutations, most women test negative and have little change in their predicted risk of breast or ovarian cancer. [3] For these women, testing may be unlikely to affect their surveillance or risk reduction regimens. Adverse psychological consequences of positive or negative tests, and employment, social or insurance discrimination are often cited as potential drawbacks to undergoing *BRCA1/2* testing. [5,6] In addition, full *BRCA1/2* testing currently costs over $2,500, and insurance coverage is variable. [7]

Currently little information is available about the uptake of *BRCA1/2* testing in a clinical setting or why women decide against undergoing testing. Most studies to date have focused on high-risk families offered testing through research protocols. [8,9] The aims of our study were to determine the proportion of women who undergo *BRCA1/2*

testing and the factors associated with decisions about *BRCA1/2* testing among women undergoing *BRCA1/2* counseling at a clinical breast cancer risk assessment program, which offers genetic testing as a clinical service.

## METHODS

### Study Setting

The University of Pennsylvania Breast and Ovarian Cancer Risk Evaluation Program (BCREP) is a multidisciplinary clinical program that provides breast cancer risk assessment, genetic counseling and genetic testing for *BRCA1/2* mutations. The program has provided clinical testing for *BRCA1/2* mutations to women without cancer since October of 1996. Although research testing is offered selectively based on eligibility criteria, clinical testing is provided to any individual who chooses to undergo testing after participating in genetic counseling. Women with an estimated probability of a *BRCA1/2* mutation less than 5% are counseled that they are unlikely to gain information from testing. During the period of this study, estimates of the probability of *BRCA1* mutation were provided using a prediction model developed by Couch et al. [10] A similar *BRCA2* prediction model did not exist at the time. Based on the population genetics of *BRCA1/2*, non-Ashkenazi women were told their risk of *BRCA2* mutation was about half that of *BRCA1*, while Ashkenazi women were told the risk was equivalent. [11] Women who are not considering undergoing *BRCA1/2* testing at the time of their visit to BCREP receive individualized information about breast and ovarian cancer risk and surveillance recommendations but do not undergo full pre-test genetic counseling.

## Study Design and Subject Selection

A total of 518 individuals participated in the Breast Cancer Risk Evaluation Program between January 1995 and April 1998. Subjects were excluded who had previously requested not to participate in further research (n=22) or were men (n=6). In October 1998, all eligible subjects (n=490) were mailed a questionnaire, letter and stamped, addressed envelope. Subjects who did not respond were mailed two reminder letters including questionnaires. The study protocol was approved by the Institutional Review Board of the University of Pennsylvania.

## Data Collection

To identify factors that were associated with decisions about genetic testing, four focus groups of women (n=16) who had participated in the BCREP were held. At each group, women were asked to list all things that had influenced their decision about genetic testing. A questionnaire was developed that asked respondents to rate the importance of each factor identified in the focus groups on a 4-point Likert response scale (very important, moderately important, a little important and not at all important). These items are listed in Table 2. In addition, the questionnaire asked subjects if they had already undergone testing, had decided to undergo testing in the future, were undecided about testing, or had decided not to undergo testing. Sociodemographic characteristics and family history of breast cancer was obtained from clinical records.

**Statistical Analysis**

Predicted lifetime risks of breast cancer for subjects without a diagnosis of breast cancer were calculated from prediction tables developed by Claus *et al.* [12] Predicted risks of *BRCA1* mutation were calculated from tables developed by Couch *et al.* from the BCREP population. [10] Because these risks had skewed distributions, the Wilcoxon rank-sum test was used in confirmatory analyses. For the primary analysis, women were characterized by self-report as having decided not to undergo testing (declined testing group) or undergoing/having undergone testing (tested group). Women who had not decided about testing were excluded. Associations between each variable and the testing decision were examined using the Wilcoxon rank-sum test for ordered variables (i.e. importance rated on a 4 point scale) and the ordinary chi-square test for dichotomous variables (e.g. very important vs. other). Multivariable analyses were conducted using multiple logistic regression. Because of correlations between concerns about health insurance, life insurance and job discrimination and between the importance of ovarian cancer risk information and importance of help deciding about prophylactic oophorectomy, composite variables were constructed to represent concern about discrimination from testing and interest in information about ovarian cancer risk. No other significant correlations were identified between variables associated with testing in this sample, including Ashkenazi background and presence of familial mutation. Each variable associated with testing in bivariate analysis at a p value of 0.10 or less was tested for inclusion in the model. The final model included all variables whose inclusion altered the odds ratio for another variable by 10% or more. Because of

concern that women might perceive the factors that influenced their decisions differently over time and according to their test results, we tested interaction terms for calendar time since counseling and *BRCA1/2* test result. To understand the factors that affected testing decisions among women at elevated risk of carrying a mutation, we repeated our analyses in the subgroup of women with a predicted probability of *BRCA1* mutation ≥ 5%.

## RESULTS

From the 490 surveys mailed, ten women had died and 36 women had moved. Three hundred and fifty three women returned completed surveys for a response rate of 80%. Non-responders did not differ from responders in age, predicted risk of breast cancer, or predicted risk of a *BRCA1* mutation in the family (p-values >0.1.). Eighteen women who were not considering undergoing *BRCA1/2* testing at the time of their visit, 76 women who were seen before *BRCA1/2* testing was offered to women without cancer outside of a research protocol and eight women who pursued testing through a research protocol were excluded from these analyses. Of the remaining 251 eligible women, 125 (50%) women had undergone *BRCA1/2* testing or were undergoing testing, 86 (34%) had decided not to undergo testing, and 40 (16%) had not decided about testing (including 14 women who had a family member pursuing testing).

The characteristics of women who underwent testing and women who decided not to undergo testing are reported in Table 1. Women who underwent testing were older and more likely to be Ashkenazi Jewish, to have a diagnosis of breast cancer and to have a known familial *BRCA1* or *BRCA2* mutation than women who declined testing.

Women who underwent testing were at slightly higher risk of breast cancer and substantially higher risk of carrying *a BRCA1* mutation than women who declined testing.

Women who underwent testing were significantly more likely to rank several potential benefits of testing as very important in their decision (Table 2). These benefits included providing cancer risk information for family members, learning information about ovarian cancer risk, help deciding about prophylactic oophorectomy and help deciding about prophylactic mastectomy. Conversely, concerns about life insurance and job discrimination were more likely to be considered very important by women who declined testing. After multivariable analyses, Ashkenazi background, known familial mutation, fear of insurance discrimination, importance of information for family members, and importance of information about ovarian cancer risk, remained associated with use of testing (Table 3). No interaction was found between the effect of these factors and calendar time since counseling or *BRCA1/2* test result (p-values >0.2).

Among the subgroup of women (n=206) with a predicted probability of a *BRCA1* mutation greater than or equal to 5%, 60 (29%) women had declined testing, 116 (56%) women had chosen to undergo testing and 30 (15%) women were undecided (including 11 women who had a family member pursuing testing). After multivariable adjustment, there were no substantial differences between the associations with testing decision in this subgroup and those found in the entire sample (data not shown).

## DISCUSSION

This study suggests that approximately two thirds of women considering *BRCA1/2* testing at the time of their visit to a clinical cancer risk evaluation program decide to undergo testing after participating in counseling. Women who undergo testing are at higher risk of carrying a *BRCA1* mutation, more likely to want information about ovarian cancer risk and for family members, more likely to be Ashkenazi Jewish, more likely to have a known familial mutation, and less likely to be concerned about insurance or job discrimination. The association with risk of *BRCA1* mutation is present whether measured by predicted probabilities, presence of familial mutation, or presence of risk factors, i.e. Ashkenazi Jewish heritage.

The associations between risk of carrying a mutation, a known familial mutation and gaining risk information for family members and decisions about *BRCA1/2* testing are reassuring. Most experts agree that *BRCA1/2* testing should be targeted to women who are most likely to gain useful information from testing. [13,14] Women at higher risk of carrying a mutation are more likely to be found to carry a mutation, more likely to gain useful information and should be more likely to decide to get tested. Women with a familial mutation will also gain more information from a negative test, as the cause of their familial predisposition has been identified. Furthermore, because of the potential implications of genetic testing for family members, more information is gained from *BRCA1/2* testing when the results are salient to other family members.

The importance of ovarian cancer risk information, and its relatively greater importance than breast cancer risk information, is likely to be multifactorial. First, prophylactic oophorectomy may appeal to more women than prophylactic mastectomy -

both because prophylactic mastectomy is a more extensive and potentially disfiguring procedure and because substantially more evidence exists supporting the efficacy of breast cancer surveillance than that of ovarian cancer surveillance. [15-17] Second, for the majority of women concerned about their increased breast cancer risk at the time they seek *BRCA1/2* counseling, finding a *BRCA1/2* mutation only confirms their belief in their increased risk. The information that testing may bring about ovarian cancer risk may seem like the bigger change. Third, *BRCA1/2* testing was the only method available to assess individual ovarian cancer risk at the time of this study, whereas several models were available to predict breast cancer risk. [18]

Although there is little evidence suggesting that insurance discrimination is occurring currently, the association between fear of insurance or job discrimination and decisions about *BRCA1/2* testing is disconcerting. Because genetic information cannot be "taken back" once received, many women are reluctant to pursue testing without assurance that discrimination could not occur in the future. This situation is particularly paradoxical if women who would have been found to carry a mutation and taken steps to lower their cancer risk decline testing because of fear of insurance discrimination. Information gained from *BRCA1/2* testing that results in women choosing interventions that lower their risk of cancer is good for everyone concerned, including life and health insurers.

This study both extends and supports the findings of prior studies of decisions about *BRCA1/2* testing. Prior studies using hypothetical scenarios generally found a majority of women reported interest in testing and interest in testing was higher among women with a higher perceived risk of carrying a mutation, greater concerns about

cancer risk, and more interest in getting information for family members. [19-24] Conversely, studies of research family members found that less than 50% of participants requested their genetic test results- however, participants requesting results also rated the benefits of testing more highly, knew more about *BRCA1* testing and had more first degree relatives with breast cancer. [8,9]

Because this study was conducted retrospectively, the decision about testing may have influenced the perceptions and reporting of the factors that were important in that decision. We cannot determine to what degree women may have adopted beliefs after they made their decision to support or justify their behavior. [25] In addition, the factors that women felt were most important in their decision about *BRCA1/2* testing may have changed over time. Establishing a single time when decisions are made about testing is difficult - in our sample, almost a fifth of women were still undecided about testing up to two years after counseling. The time point for this study was selected to minimize the number of women who had not decided about testing while maintaining reasonable proximity to the date of counseling. Although cost of testing was not an important factor in our study, our sample is highly educated and thus likely to be relatively affluent. Cost may be an important barrier to testing in less affluent populations. Finally, the generalizability of these results to women currently participating in similar programs is unknown.

**Table 1. Subject Characteristics**

| | Overall (n=211) | Testing (n=125) | Declined testing (n=86) | two tailed p-value |
|---|---|---|---|---|
| Mean age, years (range) | 44.6 (24-73) | 45.8 (24-73) | 42.7(27-73) | 0.04 |
| Caucasian (%) | 96.8 | 98.1 | 94.6 | 0.21 |
| Ashkenazi (%) | 29.9 | 42.9 | 13.3 | 0.0005 |
| College education (%) | 73.6 | 77.6 | 71.7 | 0.49 |
| Employed (%) | 74.0 | 74.1 | 77.3 | 0.72 |
| Breast CA (%) | 30.9 | 36.5 | 22.7 | 0.04 |
| Known familial mutation | 6.2 | 9.7 | 1.1 | 0.04 |
| Predicted breast CA risk,* mean (SD) | 0.24 (0.13) | 0.26 | 0.21 | 0.03 |
| Predicted BRCA1 risk,* mean (SD) | 0.18 (0.20) | 0.24 (0.23) | 0.10 (0.07) | <0.0005 |

**Table 2. Benefits, Risks and Limitations of BRCA1/2 Testing**

(Reported as proportion rating factor very important)

| | Testing (n=125) | Declined testing (n=86) | two tailed p-value |
|---|---|---|---|
| Learning about my breast cancer risk | 76.3 | 73.8 | 0.69 |
| Learning about my ovarian cancer risk | 76.1 | 57.5 | 0.005 |
| Providing information for family members | 75.8 | 56.3 | 0.003 |
| Help deciding about prophylactic mastectomy | 38.7 | 21.5 | 0.01 |
| Help deciding about prophylactic oophorectomy | 59.1 | 29.5 | 0.0001 |
| Help deciding about estrogen replacement | 29.9 | 28.8 | 0.89 |
| Desire to be reassured if test was negative | 73.9 | 69.7 | 0.52 |
| Concern about my anxiety if test was positive | 36.7 | 46.3 | 0.17 |
| Fear of health insurance discrimination | 36.1 | 47.1 | 0.11 |
| Fear of life insurance discrimination | 28.1 | 42.2 | 0.04 |
| Fear of job discrimination | 12.4 | 27.7 | 0.006 |
| Cost of the test | 22.3 | 22.9 | 0.74 |
| My doctor's recommendation | 39.3 | 32.1 | 0.30 |
| My family's recommendation | 30.7 | 30.0 | 0.96 |
| Desire to help advance research | 46.3 | 40.0 | 0.37 |

**Table 3. Adjusted Associations with UndergoingTesting (n=169)**

| | OR | 95%CI | two tailed p-value |
|---|---|---|---|
| Familial mutation | 7.46 | 0.97-62.16 | 0.06 |
| Ashkenazi background | 6.37 | 2.68-15.12 | 0.0005 |
| Importance of: | | | |
| Information for family members | 1.93 | 0.99-4.14 | 0.05 |
| Information about ovarian CA risk | 1.69 | 1.18-3.69 | 0.009 |
| Fear of insurance discrimination | 0.45 | 0.21-0.94 | 0.03 |

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Appendix K:
"Postmenopausal Hormone Replacement Therapy in Women with Hereditary Breast Cancer Susceptibility: A Decision Analysis"

# Postmenopausal Hormone Replacement Therapy in Women with Hereditary Breast Cancer Susceptibility: A Decision Analysis

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## ABSTRACT

**Background:** Women with mutations in the *BRCA1* and *BRCA2* genes are at greatly increased risk for breast and ovarian cancer. Prophylactic mastectomy and/or prophylactic oophorectomy reduce the risk of subsequent breast and ovarian cancer, respectively. The effect of postmenopausal hormone replacement therapy (HRT) on the life expectancy of women with *BRCA1/2* mutations who make alternative prophylactic surgery decisions is unknown.

**Methods:** A Markov decision analytic model used existing epidemiologic data to assess the expected outcomes of HRT in hypothetical cohorts of women with *BRCA1/2* mutations who undergo natural menopause at age 50, surgical menopause from prophylactic oophorectomy at age 40, or surgical menopause from prophylactic oophorectomy at age 30. By varying the use of prophylactic surgery and lifetime risks of coronary heart disease and osteoporosis, we evaluated the benefit of HRT in women with *BRCA1/2* mutations and alternative risk profiles. By varying the lifetime risk of breast cancer, we estimated the threshold level of breast cancer risk where HRT increases overall life expectancy, and, thus, the impact of the breast cancer risk information gained from *BRCA1/2* testing on the expected benefit of HRT. **Monte Carlo analyses were used to estimate the confidence intervals surrounding each point estimate.**

**Results:** Using this model, long-term HRT shortened life expectancy in women without coronary heart disease risk factors with *BRCA1/2* mutations undergoing natural menopause by 0.26 years (95% CI 0.54-0.00). Women with *BRCA1/2* mutations undergoing surgical menopause gained over four years from prophylactic oophorectomy. Long-term HRT decreased this gain in life-expectancy by 0.19 years (95% CI 0.43 to +0.06) in a 40 year old woman and 0.49 years (95% CI 1.58 to +0.48) in a 30 year old woman. HRT increased life expectancy by at least 0.26 years in women who underwent prophylactic mastectomy **or** and by at least 0.2 years in women who had one or more major coronary heart disease risk factors (systolic blood pressure ≥ 160, diabetes,

smoking, left ventricular hypertrophy on EKG, total cholesterol ≥ 290 or HDL ≤ 32). HRT also increased life-expectancy for all women if HRT reduced the risk of coronary heart disease by more than 65% or increased the risk of breast cancer by less than 20%. Risk of osteoporosis did not substantively affect the benefit of HRT. For women without *BRCA1/2* mutations, HRT increased life expectancy up to a lifetime breast cancer risk of 45-50%.

**Conclusions:** For women with *BRCA1/2* mutations without coronary heart disease risk factors, long-term postmenopausal HRT shortens life expectancy in the absence of prophylactic mastectomy. Although long-term HRT after prophylactic oophorectomy shortens life-expectancy compared to prophylactic oophorectomy without HRT, either strategy significantly increases life-expectancy compared to not undergoing prophylactic oophorectomy. Because identifying a *BRCA1/2* mutation increases a woman's breast cancer risk over the threshold where HRT begins to decrease life expectancy, *BRCA1/2* testing may provide useful information to women from hereditary breast cancer families considering postmenopausal HRT.

## INTRODUCTION:

*BRCA1* and *BRCA2* are the two major breast cancer susceptibility genes identified to date.(1-3) Women with mutations in either *BRCA1* or *BRCA2* have a lifetime risk of breast cancer five to eight fold higher than the population risk of 11%.(4-7) Mutations in either gene also confer a 10%-40% lifetime risk of ovarian cancer.(4-7)

Postmenopausal hormone replacement therapy (HRT) reduces the risk of osteoporosis and coronary heart disease but increases the risk of breast cancer.(8-11) The benefit of HRT appears to outweigh the risk in the general population.(12-14) However, because *BRCA1/2* mutations greatly increase the risk of breast cancer, the balance of HRT risk and benefit in women with *BRCA1/2* mutations is unclear. Furthermore, women found to carry *BRCA1/2* mutations may choose to undergo premenopausal prophylactic oophorectomy to reduce their risk of ovarian cancer and/or prophylactic mastectomy to reduce their risk of breast cancer.(15-19) Because premenopausal oophorectomy increases the risk of coronary heart disease and osteoporosis and prophylactic mastectomy decreases the risk of breast cancer, both surgeries may change the effect of HRT on life expectancy.(19-21) While the decision about HRT involves many factors in addition to its effect on life-expectancy, the specific tradeoffs of HRT among reduced coronary heart disease risk, reduced osteoporosis risk, and increased breast cancer risk have not been quantified for women with *BRCA1/2* mutations, making advising these women about HRT difficult.

Given these clinical uncertainties and the complexity of the many interrelated risks and benefits involved, the objectives of this decision analysis were to: (1) assess the expected outcomes of HRT in women with *BRCA1/2* mutations undergoing natural or surgical menopause; (2) evaluate the effect of underlying risk of coronary heart disease and osteoporosis on the benefit of HRT in women with *BRCA1/2* mutations; and (3) identify the level of breast cancer risk where

HRT no longer increases life expectancy, and, thus, the impact of the breast cancer risk information gained from *BRCA1/2* testing on the decision about HRT.

**METHODS:**

A Markov decision analytic model was constructed consisting of 722 health states ranging from perfect health to death and representing the four major diseases affected by HRT, prophylactic mastectomy or prophylactic oophorectomy: breast cancer, ovarian cancer, coronary heart disease and osteoporosis.(22) The health outcomes of a woman with a BRCA1/2 mutation adopting a particular management strategy were estimated by simulating the life span of a hypothetical cohort of women with a BRCA1/2 mutation choosing that strategy. The simulated cohort moved among health states over time according to the probability of developing disease, dying from disease or dying from other causes. Health state transition probabilities varied over time and by management strategy chosen. To calculate the primary outcome of life expectancy, the proportion of the cohort remaining alive in each annual interval was summed from age at entry until all members died or reached age 100.

**Patient Cohorts, Management Strategies and Assumptions:**

Use of HRT begins at the time of menopause. Because many premenopausal women with *BRCA1/2* mutations may undergo menopause at the time of prophylactic oophorectomy, we evaluated the expected outcomes of HRT in four cohorts: 50 year old women undergoing natural menopause; 50 year old woman undergoing prophylactic oophorectomy; 40 year old women undergoing prophylactic oophorectomy; and 30 year old women undergoing prophylactic oophorectomy. For each cohort, the impact of HRT was assessed for women who had and had not undergone prophylactic mastectomy – making a total of eight hypothetical cohorts.

Women not undergoing prophylactic mastectomy participated in semi-annual mammography, semi-annual clinical breast exam and monthly self breast exam. Decisions about ovarian cancer surveillance were not included in the model, because ovarian cancer surveillance has not been shown to alter mortality from ovarian cancer.(23-28)While tamoxifen (a selective estrogen receptor modulator) recently has been shown to reduce breast cancer risk in the absence of HRT, most experts do not consider adding HRT to tamoxifen therapy and the efficacy of tamoxifen in women with *BRCA1/2* mutations is controversial.(29-32) Women taking HRT who developed breast cancer were assumed to discontinue HRT at that time.

**Data and Health State Transition Probabilities (Tables 1 and 2):**

Data for the model were obtained from published studies of women with genetic susceptibility defined by mutation status or family history. If data were not available from these sources, model estimates were obtained from large cohort studies and meta-analyses in women unselected for risk status. A panel of local experts provided parameter estimates when no published evidence was available.

***Breast and Ovarian Cancer:*** Risks of breast and ovarian cancer in women with *BRCA1/2* mutations are controversial. Estimates from epidemiological studies of hereditary breast and ovarian cancer families suggest an 85% lifetime risk of breast cancer and 40% lifetime risk of ovarian cancer in women with *BRCA1* mutations, and 84% lifetime risk of breast cancer and 27% risk of ovarian cancer in women with *BRCA2* mutations.(5-7) However, these estimates may reflect the bias of selecting families with many cancers for linkage analysis. A cross-sectional study of the US Ashkenazi population estimated significantly lower risks of breast and ovarian cancer (60% lifetime risk of breast cancer; 14% lifetime risk of ovarian cancer) for the three mutations that comprise the vast majority of *BRCA1/2* mutations in Ashkenazi families.(4) Because it is uncertain if these lower estimates generalize to all *BRCA1/2* mutations, we used the

higher estimates from the hereditary families in our base-case analysis and examined the lower estimates in sensitivity analyses. Rates of second breast cancers were obtained from a cohort study of women with *BRCA1/2* mutations.(33) Cancer survival rates were obtained from SEER 1973-1993.(34) Sensitivity analyses considered the improved ovarian cancer survival in *BRCA1* mutation carriers documented in a recent retrospective analysis.(35)

***Coronary Heart Disease:*** Age-dependent probabilities of developing coronary heart disease for women without coronary heart disease risk factors and with alternative coronary heart disease risk profiles were calculated from a regression equation based on the 30 year follow-up of the Framingham Heart Study.(36-38) Data regarding mortality following a coronary heart disease diagnosis were obtained from the NHANES1 Epidemiologic Follow-up Survey (NHEFS) because it included data through 1987 and provided estimates stratified by age.(39) Because age-adjusted coronary heart disease mortality declined by 51% between the 1950 and 1970 Framingham female cohorts and by 37% in the US between 1979 and 1990, sensitivity analyses assessed the effect of possible improvements in survival following a diagnosis of coronary heart disease since the NHEFS.(40,41)

***Osteoporosis:*** Excess mortality from osteoporosis is largely attributable to hip fractures. Age-dependent risk of hip fracture was estimated from the NHEFS.(42) This risk is similar to that in other large cohort studies.(43-46) Incidence rates were adjusted to account for second hip fractures (assuming a 60% increase in the risk of second fracture following first fracture).(47) The mortality attributable to hip fracture was assumed to occur only in the first year after fracture.(48-52)

***Dying of Other Causes:*** The probability of dying of other causes was calculated from 1995 National Center for Health Statistics mortality statistics by adjusting age-dependent all cause

mortality for the probability of dying of breast cancer, ovarian cancer, coronary heart disease and hip fracture.(53)

***Hormone Replacement Therapy:*** Women using HRT were assumed to achieve the reduction in coronary heart disease risk observed in the case-control analysis of the Nurses Health Study.(8) This reduction is similar to that reported in other observational studies and meta-analyses, including the Iowa Women's Health Study.(54-58) The effect of HRT on hip fracture risk was obtained from the Iowa Women's Health Study, which provides estimates similar to other large cohort studies.(9, 56,59) Based on a recent randomized controlled trial of HRT in women surviving a myocardial infarction that suggested HRT may cause an early increase followed by a later reduction in mortality and an absence of data in women surviving a hip fracture, we assumed HRT did not affect mortality after a diagnosis of coronary heart disease or hip fracture.(60)

The effect of HRT on breast cancer incidence and mortality remains controversial. Most large cohort studies and meta-analyses reported an increased risk of breast cancer in women taking HRT.(10,11, 61-63) Although no specific evidence exists for women with genetic susceptibility, a single, small, case-control study suggested oral contraceptives may increase breast cancer risk in women with *BRCA1/2* mutations.(64) On the other hand, subgroup analyses of HRT and breast cancer risk in women with a family history of breast cancer have found relative risks slightly lower than those of the general population.(65,66) Although a recent analysis of the Iowa Women's Health Study suggested the increased breast cancer risk from HRT may be greatest for certain histological subtypes of invasive carcinomas with a more favorable prognosis, other cohort studies have found an increased risk among all invasive carcinomas. (10,11, 61-63) Because these data are inconclusive, the relative risk of breast cancer with use of HRT was obtained from the Nurse's Health Study, which provided estimates by duration of

use.(10) This estimate is very similar to the relative risk for invasive ductal and lobular carcinomas in women currently taking HRT for five years or less (RR 1.38) found in the Iowa Women's Health Study.(11) Because the effect of HRT on the clinical course of breast cancer is controversial and definitive empirical evidence is unavailable, use of HRT was assumed to have no effect on the clinical course of breast cancer.(61-62) All women with an intact uterus who used HRT were assumed to take progestins, which did not alter risks of coronary heart disease, osteoporosis or breast cancer, but prevented increased risk of endometrial cancer from estrogen.(69)

***Prophylactic Surgery:*** Although the reduction in cancer risk afforded by prophylactic mastectomy or prophylactic oophorectomy remains uncertain in *BRCA1/2* mutation carriers, a recent retrospective analysis of 214 women at high risk for breast cancer who underwent prophylactic mastectomy found a 90% reduction in expected breast cancer incidence.(19) A retrospective study of 12 breast/ovarian cancer families found a RR of 0.54 for ovarian cancer and 0.39 for breast cancer following prophylactic oophorectomy; however, neither estimate was statistically significant.(18) A preliminary analysis of a cohort of women with *BRCA1* mutations undergoing prophylactic oophorectomy found a RR of 0.22 (95% CI 0.12-0.41) for subsequent breast cancer incidence.(70) Based on these figures, we assumed that prophylactic mastectomy afforded a 90% reduction in breast cancer incidence and prophylactic oophorectomy a 50% reduction in ovarian cancer incidence. Women who did not take HRT following prophylactic oophorectomy were assumed to have a 60% decrease in the incidence of breast cancer from the time of surgery until the time of natural menopause (age 50) and a two fold increase in risk of coronary heart disease and hip fracture.(20,21, 70,71) Women who took HRT following prophylactic oophorectomy were assumed to have no increase in coronary heart disease or osteoporosis risk, and to modify the reduction in breast cancer risk by the increase in breast

cancer risk from HRT. Surgical mortality was assumed to be equivalent to that of general anesthesia (3/10,000) for bilateral prophylactic mastectomy with concurrent reconstruction or bilateral prophylactic oophorectomy in this relatively young, healthy cohort of women.(72,73)

***Routine Surveillance:*** Because it is recommended that mammography screening begin before the age of 50 and the risk reduction from mammography in women under 50 is less than in women over 50, the relative risk reduction from mammography in women with *BRCA1/2* mutations may be less than in average risk women over the age of 50.(16, 74,75) However, increased frequency of screening, potentially higher compliance, and increased use of alternative modalities (such as MRI) may improve effectiveness.(16, 76) Thus, the overall benefit of more frequent breast cancer surveillance in this population was assumed to be equivalent to that of routine mammography in average risk women over 50.(77)

**Estimating Uncertainty:**

***Monte Carlo Analysis:*** To determine the distribution of possible outcomes from HRT, Monte Carlo analyses were conducted for the comparison of HRT vs no HRT for each of the eight hypothetical cohorts. For each Monte Carlo analysis, the computer randomly assigned values to each transition probability according to their probability distributions. Probability distributions were derived from the published literature and were assumed to be normal unless otherwise specified. (Table 2) Iterative analyses (n=250) were conducted to estimate the 95% confidence interval around the point estimate of the change in life expectancy from HRT. Probability distributions were not included for risks of coronary heart disease and osteoporosis (that vary according to a woman's risk factors) but were included for the risks of breast and ovarian cancer that were derived from epidemiologic studies of *BRCA1/2* mutation carriers.

***Sensitivity Analyses:*** One way and two way sensitivity analyses were conducted to assess the effect of alternative coronary, osteoporosis and breast cancer risk factor profiles on the benefit of HRT and to estimate the thresholds where the overall benefit might change.

**RESULTS:**

***50 year old woman without coronary heart disease risk factors undergoing natural menopause (Table 1):***

In the absence of prophylactic surgery, our model predicts that long-term use of HRT in a 50 year old woman with a *BRCA1/2* mutation without coronary heart disease risk factors is associated with decreased life expectancy of 0.26 years (95%CI 0.54-0.00). For these women, the increased risk of early breast cancer from HRT outweighs its long-term benefit in reducing coronary heart disease and osteoporosis (Figure 2). Similarly, a 50 year old woman with a *BRCA1/2* mutation who has undergone prophylactic oophorectomy without prophylactic mastectomy is predicted to lose 0.31 (95% CI 0.66 to +0.05) years of life expectancy with long-term HRT. However, if she has undergone prophylactic mastectomy (with or without prophylactic oophorectomy), HRT increases life expectancy by 0.58 (95% CI 0.35 to 0.82) and 0.48 (95% CI 0.31 to 0.70) years respectively. The decrease in breast cancer risk afforded by prophylactic mastectomy shifts the balance of risk and benefit to favor the cardioprotective effects of HRT.

***30 year old or 40 year old woman without coronary heart disease risk factors undergoing prophylactic oophorectomy (Table 1):***

In our model, long-term HRT decreases life expectancy in women with a *BRCA1/2* mutation who underwent prophylactic oophorectomy at age 30 or age 40 by 0.49 (95% CI 1.58 to +0.48) and 0.19 (95% CI 0.43 to +0.06) years respectively. However, prophylactic

oophorectomy with long-term HRT is still associated with a substantial increase in life expectancy (over 4 years) compared to not undergoing prophylactic oophorectomy. In 30 or 40 year old women with *BRCA1/2* mutations without coronary heart disease risk factors undergoing prophylactic oophorectomy, the increased risk of breast cancer attributable to HRT more than offsets the resulting reduction in coronary heart disease and osteoporosis risks but does not negate the overall gain in life expectancy associated with prophylactic oophorectomy. In contrast, HRT increases life expectancy 1.74 (95% CI 0.74 to 2.73) and 1.16 (95% CI 0.93 to 1.42) years respectively for 30 and 40 year old women undergoing prophylactic oophorectomy in conjunction with prophylactic mastectomy.

**Sensitivity Analyses:**

Sensitivity analyses had very little effect on the benefit of HRT in women with *BRCA1/2* mutations who underwent prophylactic mastectomy or both prophylactic mastectomy and prophylactic oophorectomy, irrespective of coronary heart disease risk. For these women, HRT increases life expectancy across the range of values examined, including a risk reduction from prophylactic mastectomy as low as 50%. Furthermore, varying the risk of osteoporosis, the efficacy of prophylactic oophorectomy or the efficacy of ovarian cancer screening has no substantive impact on the overall effect of HRT in any of the management strategies. Decreasing the risk of ovarian cancer (either incidence or mortality) slightly decreases the benefit of HRT for all management strategies. However, for women with *BRCA1/2* mutations not choosing prophylactic mastectomy, sensitivity analyses identified other variables where the effect of HRT on life expectancy became beneficial.

***Coronary heart disease risk:*** The impact of HRT on life expectancy depends upon the underlying risk of coronary heart disease (Figure 3). As the risk of coronary heart disease increases, the benefit of HRT increases. Women with a *BRCA1/2* mutation and a lifetime risk of

coronary heart disease greater than 50% experience an increase in life expectancy with HRT whether or not they undergo prophylactic mastectomy.

***Breast cancer risk:*** The impact of HRT also depends upon the underlying risk of breast cancer (Figure 4). As the risk of breast cancer decreases, the benefit of HRT increases. HRT begins to increase life expectancy when the risk of breast cancer falls below 50% in the setting of no prophylactic surgery and 45% in the setting of prophylactic oophorectomy. If the lower, population-based estimates of breast and ovarian cancer incidence in *BRCA1/2* mutation carriers (60% lifetime risk of breast cancer and 14% lifetime risk of ovarian cancer) are used, HRT continues to decrease life expectancy in women who do not undergo prophylactic mastectomy, however, the decrement is small (0.14 years).

***Effect of HRT on coronary heart disease or breast cancer:*** The degree to which HRT reduces the risk of coronary heart disease or increases the risk of breast cancer significantly affects the overall impact of HRT on life expectancy. If HRT reduces the risk of coronary heart disease more than 65% or increases the risk of breast cancer less than 20%, HRT is beneficial for all women irrespective of coronary risk or use of prophylactic surgery.

***Efficacy of breast cancer surveillance:*** If breast cancer surveillance reduces breast cancer mortality more than 65%, HRT increases life expectancy for all women.

**DISCUSSION:**

Use of postmenopausal HRT is a difficult decision for many women because of the complexity of the associated risks and the fear of breast cancer. For women at increased risk of breast cancer, the decision can be particularly challenging because the net life expectancy benefit of HRT becomes less certain. For women with *BRCA1/2* mutations who may also be considering prophylactic surgery, the HRT decision is even more complex. The number of factors and

information that must be simultaneously considered overwhelms intuitive, subjective decision-making. A decision model that incorporates both the existing empirical evidence and the uncertainty of these estimates, thus, can yield important and useful information about the expected outcomes of alternative choices to help guide patient and physician decision making.

For women with *BRCA1/2* mutations, the impact of HRT on life expectancy is primarily a function of their decision about prophylactic mastectomy and their underlying risk of coronary heart disease. A woman at low risk of coronary heart disease who chooses not to undergo prophylactic mastectomy will experience a net loss of life expectancy with long-term HRT when initiated at the time of natural or surgical menopause. If she chooses to undergo prophylactic mastectomy or has a 50% or higher lifetime risk of developing coronary heart disease (compared to the 30% lifetime risk of coronary heart disease in our base-case analysis), long-term HRT increases life expectancy by half a year or more, regardless of whether menopause is natural or surgical. Data from large cohort studies can be used to translate this 70% **relaixxxx** increase in coronary heart disease risk into risk factor profiles.(39,78) According to the Framingham Heart Study, presence of systolic blood pressure over 160, diabetes, left ventricular hypertrophy on EKG, total cholesterol $\geq 290$ or HDL $\leq 32$ confers a 70% increase in coronary heart disease risk.(78) NHEFS also suggests current smoking increases coronary heart disease risk by 80%.(39) Women with *BRCA1/2* mutations and any one of these risk factors can expect to experience increased life expectancy from HRT.

While use of prophylactic mastectomy and risk of coronary heart disease currently have the greatest impact on the expected outcomes of HRT, other factors may alter the balance of risk and benefit in the future. New techniques that may improve breast cancer screening diagnostic sensitivity, such as MRI, are being studied in high-risk women.(76) If improved early detection

can reduce breast cancer mortality by more than 65%, HRT would extend life expectancy for all women with *BRCA1/2* mutations, even in those not undergoing prophylactic mastectomy.

This analysis identified a breast cancer risk threshold of 50% below which women without coronary heart disease risk factors are expected to gain increased survival from HRT. Several models are currently available to predict breast cancer risk on the basis of family, reproductive, and breast disease history.(79,80) In the absence of a *BRCA1/2* mutation, few combinations of risk factors increase breast cancer risk to 50% or greater. According to the Gail model (used to determine eligibility for the tamoxifen breast cancer prevention trial), a woman has to have two or more first degree relatives with breast cancer and two or more breast biopsies to reach a lifetime breast cancer risk over 50%.(79) According to the tables developed by Claus *et al.* from the Cancer and Steroid Hormone Study, no combination of family history (including two first degree relatives diagnosed under the age of 30) predicts a lifetime breast cancer risk over 50%.(80) Thus, in the absence of a *BRCA1/2* mutation, HRT can be expected to increase life expectancy in the overwhelming majority of women with a family history of breast cancer. For these women, *BRCA1/2* testing can provide important information that bears directly upon HRT decisions. In the absence of coronary heart disease risk factors, a positive *BRCA1/2* test will raise breast cancer risk to the level where HRT is predicted to decrease life expectancy, while a negative *BRCA1/2* test leaves breast cancer risk at a level where HRT is predicted to increase life expectancy. This information may be useful to many women with a family history of breast cancer who are considering HRT.

Previous decision analyses in women at average breast cancer risk have found HRT increases life expectancy by half a year in a woman at average coronary heart disease risk and up to three and a half years for women with several coronary heart disease risk factors.(12-14) The estimate of half a year increase in low risk women is very similar to our estimate (+ 0.48 years)

in a 50 year old woman with a *BRCA1/2* mutation at low risk of coronary heart disease who underwent prophylactic mastectomy (which is estimated to decrease her breast cancer risk from 85% to approximately the general population risk). One recent decision analysis evaluating the effect of breast cancer risk on the benefit of HRT found that all women would gain life expectancy from HRT except women at low coronary heart disease risk with two or more first degree relatives with breast cancer. Our analysis identifies a slightly higher threshold for the benefit of HRT (two first degree relatives and two breast biopsies). This difference is most likely attributable to our use of more recent, age-dependent data showing improved survival following a diagnosis of coronary heart disease.(39)

Our study also provides some insight into the potential impact of prophylactic mastectomy and oophorectomy (irrespective of HRT). Increases in life expectancy from prophylactic surgery are greatest for young women, women undergoing both mastectomy and oophorectomy, and higher estimates of cancer risk and surgery benefit. Although use of longterm HRT after prophylactic oophorectomy slightly shortens life-expectancy compared to prophylactic oophorectomy without HRT, either strategy significantly increases life-expectancy compared to not undergoing prophylactic oophorectomy. Thus, women considering postponing prophylactic oophorectomy because of concerns of postmenopausal symptoms may be reassured that even with the addition of HRT, the gain in life expectancy from prophylactic oophorectomy is substantial. Our estimates are slightly higher than a previous decision analysis of prophylactic surgery, which found prophylactic mastectomy results in a gain of life expectancy of 5.3 years and prophylactic oophorectomy of 1.7 years in a 30 year old woman with a BRCA1/2 mutation.(81) These differences can be attributed to our ability to incorporate recently published data, including higher breast cancer risk reduction from prophylactic mastectomy, significant

reduction in breast cancer risk from prophylactic oophorectomy, and to our use of more conservative estimate of the benefits of breast cancer surveillance. (19,70,77)

The primary limitations of this analysis arise from the inevitable uncertainty about many of the needed data estimates. Because the ability to identify women with *BRCA1/2* mutations is a recent development, the risk of HRT, the clinical course of breast and ovarian cancer, and the benefit of routine surveillance and prophylactic surgery are not known precisely for women with mutations in these genes. Furthermore, the true penetrance of *BRCA1* or *BRCA2* mutations remains controversial and may be mutation dependent. Lower estimates of breast cancer penetrance would improve the benefit of HRT; higher estimates reduce its benefit and increase its risk. The Monte Carlo analyses suggest the impact of this uncertainty on the decision about HRT is greatest for women who undergo prophylactic oophorectomy alone and least for women who undergo prophylactic mastectomy with or without oophorectomy. For women undergoing prophylactic mastectomy, HRT uniformly increases life expectancy across the 95% confidence intervals. For 50 year old women who undergo natural menopause without oophorectomy or mastectomy, HRT decreases life expectancy but the 95% confidence interval includes the possibility that HRT would neither decrease nor increase life expectancy. For women who undergo prophylactic oophorectomy at age 30, 40 or 50, the point estimates suggest HRT will decrease life expectancy but the 95% confidence intervals include the possibilities that HRT could increase life expectancy by 0.05 to 0.48 years. As all women with BRCA1/2 mutations still face the difficult decision about HRT without the benefit of definitive epidemiologic data, the information provided by decision analysis may provide the best assistance available. In fact, it is in the setting of significant risk and uncertainty that decision models may be most helpful.(82) However, it is particularly important to convey the significant degree of uncertainty about these estimates when counseling individual patients.

Decisions about HRT involve many factors in addition to life expectancy. Quality of life can be both positively and negatively affected by HRT.(83-85) Symptomatic benefits of HRT, which are extremely important to some women, are not captured in an analysis of life expectancy alone. Conversely, more than 50% of women who begin HRT stop taking it within five years, primarily because of vaginal bleeding and breast tenderness.(86) Anxiety about increasing the risk of breast cancer also may reduce the benefit from HRT for many women. While we did not include quality adjustments in our assessment of health outcomes because our primary interest was in providing life-expectancy information to women and the methodology of utility measurement is evolving, decisions about HRT ultimately must be guided by a woman's preferences, values and attitudes towards risk.(87,88) For many women, the best decision about HRT may not be the one that maximizes life expectancy.

Despite these limitations, this study provides important information for women with hereditary breast cancer susceptibility considering HRT. For women with *BRCA1/2* mutations who undergo prophylactic mastectomy or have coronary heart disease risk factors, HRT will increase life expectancy. However, for women with *BRCA1/2* mutations who choose not to undergo prophylactic mastectomy, HRT decreases life expectancy in the absence of coronary heart disease risk factors. Thus, for women without coronary heart disease risk factors from hereditary breast cancer families, *BRCA1/2* testing may provide important information about breast cancer risk for guiding decisions about HRT. Finally, this study suggests that BRCA1/2 carriers who choose prophylactic oophorectomy may take HRT and retain most of the survival benefit of that procedure. While we await the results of large scale randomized trials of HRT, women from hereditary breast cancer families continue to face the especially difficult decision about postmenopausal HRT. The results of this analysis provide evidence to better inform these decisions and may make counseling these women a little easier.

**Table 1. Disease Incidence and Survival**

| | Base-Case Value | Sensitivity Analysis Range | Source(s)* |
|---|---|---|---|
| **Breast cancer** | | | |
| Incidence | 0.85 lifetime | 0.10-0.90 | 4,5,**6**,7 |
| Mortality | 0.025 first yr<br>0.032 subsequent yrs | 0.01-0.05 | **34** |
| **Ovarian cancer** | | | |
| Incidence | 0.40 lifetime | 0.10-0.60 | 4,5,**6**,7 |
| Mortality | 0.76 @ 5 yrs | 0.40-0.80 | **34,** 35 |
| **Coronary heart disease** | | | |
| Incidence | 0.32 lifetime | 0.30-0.90 | **36,37,38** |
| Mortality | 0.1-0.3 first yr | 0.05-0.4 | **39** |
| | 0.01-0.04 subsequent yrs | 0.005-0.08 | |
| **Hip fracture** | | | |
| Incidence | 0.20 lifetime | 0.10-0.40 | **42**,43,44,45,46 |
| Mortality | 0.17 first yr | 0.08-0.35 | **48**,49,50,51,52 |

* References in bold represent values used in base-case analysis

**Table 2. Effect of Interventions on Disease Incidence**

| | Relative Risk | Sensitivity Analysis Range | Source(s)* |
|---|---|---|---|
| **HRT** | | | |
| Coronary heart disease | 0.5 | 0.3 - 0.8 | **8**,54,55,56,57,58 |
| Breast cancer | 1.12 for 1-2 yrs<br>1.20 for 3-4 yrs<br>1.46 for > 5 yrs | 1.0 - 2.5 | **9**,11,61,62,63,<br>64,65,66 |
| Osteoporosis | 0.58 | 0.3 - 0.8 | **10**,56,59 |
| **Prophylactic mastectomy** | | | |
| Breast cancer | 0.1 | 0.05 - 0.8 | **19** |
| **Prophylactic oophorectomy** | | | |
| Ovarian cancer | 0.5 | 0.1 - 0.9 | **18** |
| Breast cancer | 0.4 | 0.5 - 1.0 | **18**, 70 |
| Coronary heart disease | 2.0 | 1.0 - 2.5 | **21** |
| Osteoporosis | 2.0 | 1.0 - 2.5 | **20** |
| **Surveillance** | | | |
| Breast cancer mortality | 0.7 | 0.35 -1.0 | **74**,75,77 |
| Ovarian cancer mortality | 1.0 | 0.7 - 1.0 | **23**,24,25,26,27,28 |

* References in bold represent values used in base-case analysis

**Table 3. Change in Life Expectancy with Use of HRT in Women with a *BRCA1/2* Mutation and No Coronary Heart Disease Risk Factors**

| | LE | Change in LE with HRT | 95% CI | Proportion of Simulations where HRT Increased LE |
|---|---|---|---|---|
| **50 year old** | | | | |
| No surgery | 74.41 | -0.26 | -0.54 to 0.00 | 5% |
| PO* | 76.45 | -0.31 | -0.66 to +0.05 | 8% |
| PM* | 77.55 | +0.48 | +0.31 to +0.70 | 100% |
| PO and PM | 80.05 | +0.58 | +0.35 to +0.82 | 100% |
| **40 year old** | | | | |
| No surgery | 66.58 | - | - | |
| PO | 71.05 | -0.19 | -0.43 to +0.06 | 11% |
| PM and PO | 75.27 | +1.16 | +0.93 to +1.42 | 100% |
| **30 year old** | | | | |
| No surgery | 61.18 | - | - | |
| PO | 65.94 | -0.49 | -1.58 to +0.48 | 22% |
| PM and PO | 71.77 | +1.74 | +0.74 to +2.73 | 100% |

*PO= prophylactic oophorectomy, PM= prophylactic mastectomy

**Figure 1. Cumulative Incidence of Breast Cancer and Coronary Heart Disease***

*Estimated from simulation model

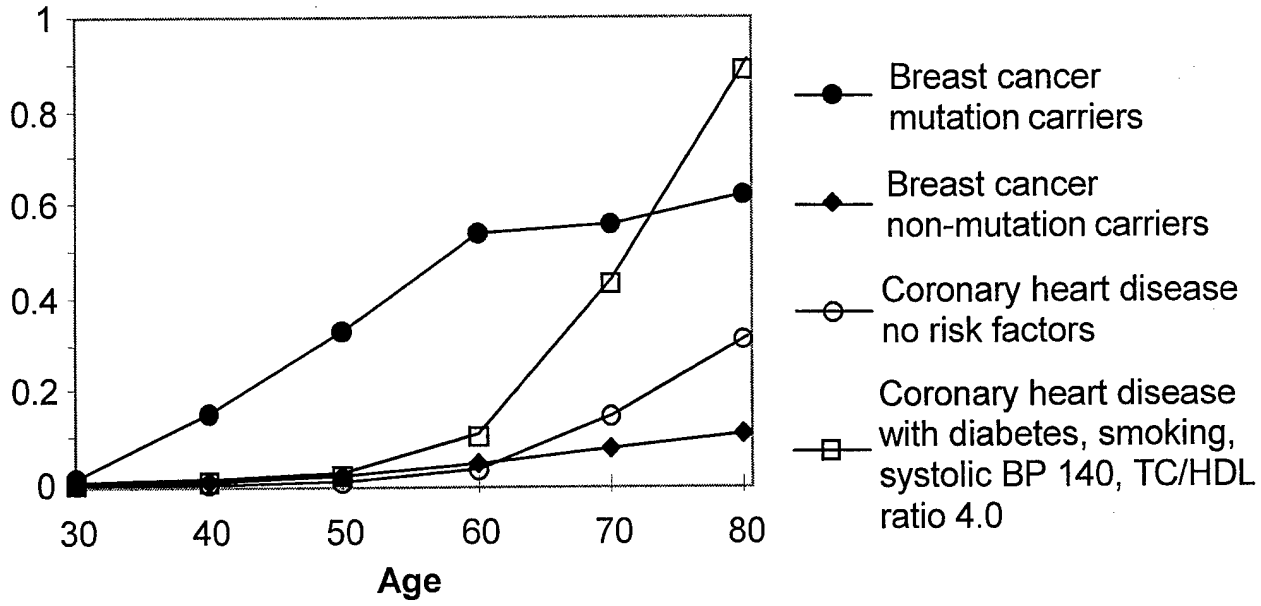

1
0.8
0.6
0.4
0.2
0
30
40
50
60
70
80
Age
Breast cancer mutation carriers
Breast cancer non-mutation carriers
Coronary heart disease no risk factors
Coronary heart disease with diabetes, smoking, systolic BP 140, TC/HDL ratio 4.0

**Figure 2. Change in Life Expectancy with Use of HRT in a 50 Year Old Woman with *BRCA1/2* Mutation without Prophylactic Mastectomy or Prophylactic Oophorectomy According to Coronary Heart Disease Risk**

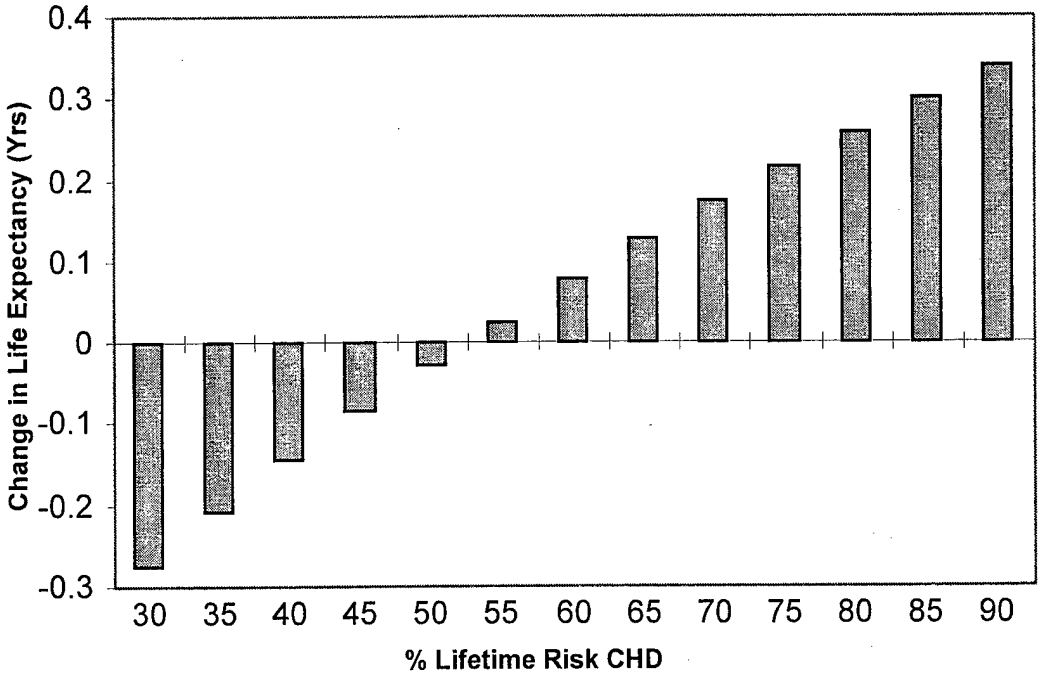
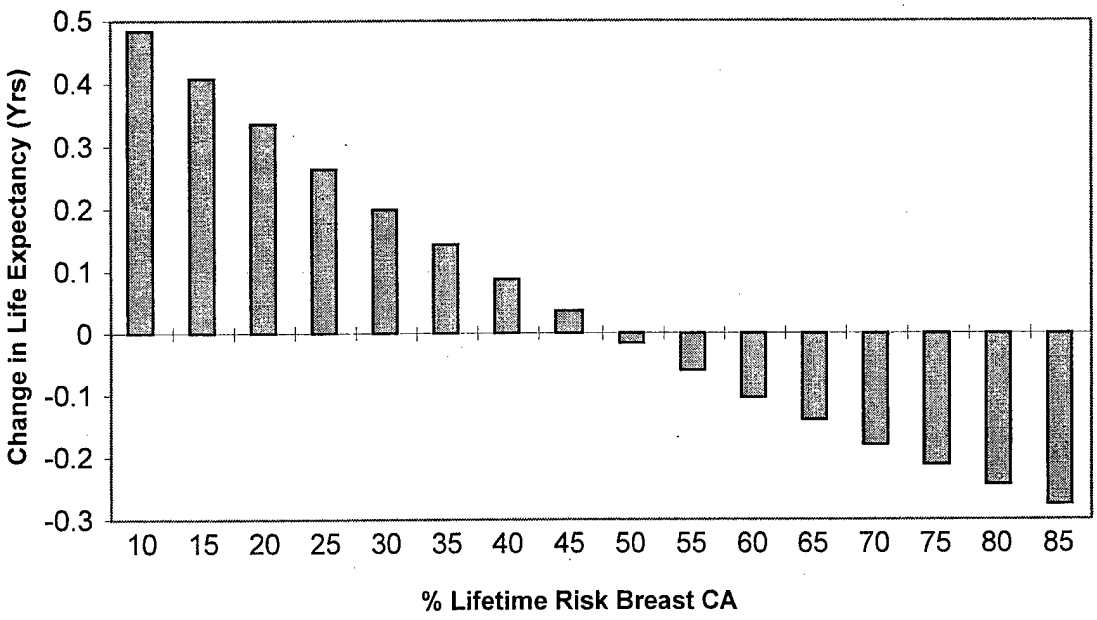

0.4
0.3
0.2
0.1
0
-0.1
-0.2
-0.3
Change in Life Expectancy (Yrs)
30
35
40
45
50
55
60
65
70
75
80
85
90
% Lifetime Risk CHD

**Figure 3. Change in Life Expectancy with Use of HRT in a 50 Year Old Woman without Coronary Heart Disease Risk Factors without Prophylactic Mastectomy or Prophylactic Oophorectomy According to Breast Cancer Risk**


0.5
0.4
0.3
0.2
0.1
0
-0.1
-0.2
-0.3
Change in Life Expectancy (Yrs)
10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85
% Lifetime Risk Breast CA

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## Appendix L:
## "Comprehension of Survival Curves by the General Public"

## RISK OF VERY LOW BIRTHWEIGHT IF PRENATAL CARE IS INADEQUATE

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Birth at very low birthweight (VLBW: less than 1500 grams) is the greatest predictor of infant mortality (death by the age of one year); this study asks: Does inadequate prenatal care affect an infant's risk of being born at VLBW?

This research adds to the literature an analysis of individual infant risk of birth at VLBW. Data (N=50,568) are randomly sampled from vital statistics for a one-year U.S. birth cohort (about 4 million); these represent the 50 states and DC. Controls are: 3 dichotomies for infant race – African-American (AFRO), Caucasian (CAUC), All Others (OTHR); 2 continuous variables for maternal age & schooling; 1 dichotomy for marital status (ONEPAR). The independent test variable – inadequate prenatal care (PCINADQ) – is dichotomous, with inadequate defined as no care, third trimester start, or too few visits. The dependent variable is dichotomous – birth at VLBW or above. Logistic regression analyzes the log odds of birth at VLBW if prenatal care is inadequate; the equation controls for infant race and the parental factors.

Results show that PCINADQ predicts an 80% increase in risk of VLBW birth. This is greater than the ONEPAR effect, which increases risk by 35%. Neither of these results differ by infant race. VLBW risk decreases significantly overall with greater maternal schooling, but this protective effect is found to be diminished among AFRO infants. Risk also decreases significantly with younger maternal age, but only among AFRO infants.

In conclusion, inadequate prenatal care is the most important variable found here to increase the risk of VLBW birth; it is more influential than any of the parental risk factors tested. Further research is needed to study: (1) the interactive effects of maternal age/schooling with inadequate prenatal care on VLBW risk and (2) the unexpected finding that older maternal age increases risk among African-Americans. Health policy, whether public or private, needs to remove barriers to adequate prenatal care – it is important to note that barriers may differ by race or maternal age/schooling. The basic efficiency of prenatal health care is this: provision of adequate prenatal care to one mother predicts healthier birth outcomes for both her infant(s) and for herself.

## COMPREHENSION OF SURVIVAL CURVES BY THE GENERAL PUBLIC

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Background: The use of survival and mortality curves is a promising tool to help patients understand complex treatment choices. Comprehension of risk information by the general public is limited and subject to framing effects. However, the ability to comprehend survival curves has not been established.

Objective: Determine how well the general public comprehends survival curves, if comprehension is improved by adding an introductory single curve and if it depends upon presenting outcomes as survival, mortality, or survival and mortality curves.

Methods: Sequential self-administered surveys randomized prospective jurors to alternative survival curve formats. All formats described treatment effect on 100 hypothetical individuals using two survival curves. Comprehension was measured by the ability to report number of people alive and difference in number alive at different times according to treatment.

Results: The 696 respondents had a mean age of 41, mean 14 years of education, were 41% African-American, and 66% women. Ability to report number of people alive was high and improved with an introductory single curve (83 vs 74% accurate, p=0.03). However, ability to calculate survival differences between curves was lower and did not differ (55 vs 55% accurate, p=0.89). Similarly, ability to report number alive was higher with presentation as survival curves or survival and incidence curves than as incidence curves (73 vs 73 vs 56% accurate, p=0.01), but ability to calculate survival differences remained low for all three presentations (54 vs 61 vs 50% accurate, p=0.16). Many respondents treatment choices were intransitive: for example, some willing to undergo surgery for 5% improvement in survival were unwilling for 20% improvement.

Conclusions: Most of the general public can report survival rates from a survival curve and this simple comprehension is improved by the use of a single curve introduction and presentation as survival rather than incidence curves. However, in self-administered surveys, many members of the general public cannot manipulate or interpret the information contained in survival curve comparisons to aid with treatment choice.

## ONE-THOUSAND HEALTH-RELATED QUALITY OF LIFE ESTIMATES

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Objective: Toward the goal of creating a national repository of health-related quality of life (QOL) weights as suggested by the Panel on Cost-Effectiveness in Health and Medicine (Gold et al, 1996), we amassed more than 1000 QOL weights and assessed the range and nature of this publicly available data.
Methods: QOL data were drawn from publicly available documents identified through review articles, databases such as MEDLINE and the NHS Economic Evaluation Database, as well as other sources. Only original QOL estimates evaluated on a 0-1 scale were included. We extracted key information from each source including a description of the health state, QOL weight, QOL standard deviation, the method used to elicit the weights (e.g. standard gamble) or derive them indirectly (e.g. EuroQol), lower and upper bounds of the scale (e.g. death to perfect health), and the number and type of persons interviewed.
Results: We identified 155 source documents yielding 1,019 original QOL weights. There was considerable variation in the QOL weights reported for identical health states. For example, QOL for major stroke ranged from 0.2 to 0.5, myocardial infarction (with no qualifiers) ranged from 0.68 to 0.9, and AIDS (again with no qualifiers) ranged from 0.24 to 0.79. Some variation is likely due to the choice of upper and lower bounds of QOL scales, assessment methods, or the population surveyed. Additional variation was due to factors such as the stage of illness. For example, QOL for stroke ranged from 0.03 to 0.92 depending on the severity of subsequent language, cognitive, or motor deficits.
Conclusions: QOL weights reflect the desirability of health states and are useful in determining the cost-effectiveness of treatments and policies. However, this research indicates that there is significant heterogeneity among published QOL weights. When inconsistent weights are used in cost-utility analyses, the comparability of these analyses is impaired. This preliminary repository of QOL weights will enable analysts to review the full range of studies offering QOL estimates for a given disease, aid their selection of QOL weights from the literature, and thus improve the quality of analyses upon which resource decisions are based.

## WHAT IS THE COST-UTILITY OF POST-POLYPECTOMY COLONOSCOPIC SURVEILLANCE STRATEGIES IN PERSONS WITH A FAMILY HISTORY OF COLORECTAL CANCER?

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Persons with a family history of colorectal cancer (CRC) in a first-degree have a risk of developing CRC that is approximately double that of the standard-risk population. The number of adenomas (Ad) found on initial colonoscopy may also be used to stratify persons as to their risk of developing future colorectal neoplasia (CRN). We examined the cost-utility (C/U) of post-polypectomy colonoscopic surveillance (PPCS) in persons with an affected first-degree relative using our discrete-event simulation model of the natural history of CRN. QALYs were computed as the measure of effectiveness. We created hypothetical cohorts consisting of 100,000 persons of each combination of gender and Ad count on initial colonoscopy (1, 2, >2). Each cohort was drawn from a population with double the mean underlying risk of developing Ad at any given age compared to the standard-risk population. We modeled each PPCS strategy to calculate its C/U. Each simulated person was screened initially at age 40 and then the PPCS strategy was followed until death. We discounted both costs and QALYs at a 3% annual rate.

| | Female marginal C/U ($/QALY) | | | Male marginal C/U ($/QALY) | | |
|---|---|---|---|---|---|---|
| Strategy | 1Ad | 2 Ad | >2 Ad | 1Ad | 2 Ad | >2 Ad |
| q10 | - | - | - | - | - | - |
| q3/10 | 39,333 | 15,667 | dominated | dominated | dominated | dominated |
| q7 | 101,000 | 16,750 | 9,233 | 38,500 | 16,706 | 8,393 |
| q3/7 | 104,500 | 35,667 | 31,000 | dominated | 30,714 | 19,364 |
| q3/5 | 294,000 | 141,500 | 71,500 | 308,500 | 389,000 | 65,333 |

The mean results are shown above. The label "q3/10" means survey every 3 years until <2 Ad are found then switch to every 10 years surveillance. The "no surveillance" strategy was always dominated by the q10 strategy. Sensitivity analyses revealed that a lower cost of colonoscopy, a lower sensitivity of colonoscopy, and a lower discount rate might justify more frequent surveillance. In persons with a family history of CRC initially screened at age 40, PPCS using an every 10 year strategy was always cost-effective compared to no surveillance. Other PPCS strategies may be cost-effective depending on person gender, number of Ad found at initial colonoscopy, and societal willingness to pay.

## DOES THE CHOICE OF PSYCHOMETRIC, CLINIMETRIC, UTILITY, OR ADHERENCE OUTCOMES INFLUENCE CONCLUSIONS IN A HEARING AID TRIAL?

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Purpose: With advances in hearing aid technology resulting in increasingly expensive products, decision makers face growing challenges in allocating resources to hearing impaired patients. We sought to determine how conclusions about treatment effectiveness are altered by the choice of outcomes measures.

Methods: As part of a project to study the cost-effectiveness of hearing amplification, an ongoing randomized pilot trial at the Seattle Veterans Hospital has enrolled 48 veterans with sensorineural hearing loss into one of four treatment arms: no amplification, an assistive listening device ("PocketTalker"), a conventional hearing aid, and a deluxe aid. Structured and open-ended data about quality of life (QOL), health status, utility, and adherence were collected at baseline, 1 month and 3 months.

Results: Clear treatment distinctions have been observed. The Hearing Handicap Inventory for the Elderly (QOL scale ranging from 0 to 100) improved 41 points in the deluxe arm (P<.001), 13 points in the conventional arm (P<.001), and only 5 and 1 points (P>.05) in the PocketTalker and control arms at 1 month. A clinimetric approach, using a taxonomy of quality of life issues to compare open-ended diary and questionnaire data, also revealed clear distinctions. For example, all patients with deluxe aids had better speech understanding, and none had complaints. Patients with conventional aids reported improved speech understanding in quiet, but 40% had difficulty in background noise. Few PocketTalker patients reported favorably, and the majority (75%) had difficulty with background noise. Similar trends were noted in emotional, social, and convenience domains. However, generic health status (SF-36) and utility measures (HUI, willingness to pay, and computerized standard gamble, time trade-off, and rating scale techniques) have failed to differentiate treatment effects. Adherence data failed to distinguish between hearing aids (7.7 and 8.6 hours/day, deluxe and conventional arms), although PocketTalker use was significantly lower (<1 hour/day).

Conclusions: Disease-specific and open-ended data strongly suggest that patients prefer sophisticated technology, but utility-based measures do not detect differences in outcome. These findings have strong implications about the methods used to make decisions about resource allocation.

## DIAGNOSTIC IMAGING OF PERIPHERAL ARTERIAL OCCLUSIVE DISEASE: A META-ANALYSIS OF GADOLINIUM-ENHANCED MAGNETIC RESONANCE ANGIOGRAPHY AND COLOR-GUIDED DUPLEX ULTRASONOGRAPHY

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Purpose: To summarize and compare the published data on gadolinium-enhanced magnetic resonance angiography (MRA) and color-guided duplex ultrasonography for the workup of peripheral arterial occlusive disease.

Methods: An English-language literature search of studies published between January 1984 and November 1998 was performed. Additional references were obtained from bibliographies of reviews and original papers, and experts in the field were consulted. Two reviewers independently extracted the data and discrepancies were resolved by consensus. Papers were included if: 1)gadolinium-enhanced MRA and/or color-guided duplex ultrasonography were performed for the workup of peripheral arterial occlusive disease; 2) contrast (x-ray) angiography was used as the reference test; 3) absolute numbers of true positives, false negatives, true negatives and false positives were available or derivable.

Results: Nine articles on MRA and 18 articles on duplex were included in the baseline-analysis. Based on a random effects model the pooled sensitivity for MRA (97.5% (95% CI, 95.7%-99.3%) ) was higher than that for duplex (87.6% (95% CI, 84.4%-90.8%)). The pooled specificities were very similar (96.2% (95% CI, 94.4%-97.9%) for MRA and 94.7% (95% CI, 93.2%-96.2%) for duplex). Summary receiver operating characteristics analysis demonstrated that MRA had a better discriminatory power than duplex (regression-coefficient of MRA vs. duplex: 1.67 (95% CI, -0.23 to 3.56) with and 2.11 (95% CI, 0.12 to 4.09) without adjustment for covariates).

Conclusions: The results suggest that gadolinium-enhanced MRA has a better discriminatory power than color-guided duplex ultrasonography and is a highly sensitive and specific test compared to contrast x-ray angiography for the workup of peripheral arterial occlusive disease.

Appendix M:
"Breast Cancer Risk Perception and Use of Postmenopausal Hormone Replacement Therapy"

RACIAL DISPARITY IN THE CLINICAL MANAGEMENT OF ACUTE MYOCARDIAL INFARCTION. J. Allison, C. Kiefe, N. Weissman, J. Canto, R. Centor, R. Farmer. Dept of Medicine. University of Alabama at Birmingham.

**Background:** Much has been written about racial disparities in the management of cardiovascular disease, especially regarding invasive procedures such as angioplasty and coronary artery bypass grafting. Less is known about racial disparities in the medical management of cardiovascular disease. Therefore, we sought to compare the medical treatment of African American and White Medicare patients with acute myocardial infarction (AMI) using an existing national data set.

**Methods:** Centrally-trained abstractors established the Cooperative Cardiovascular Project data set by retrospective medical record review of a proportional sample of Medicare admissions from 6,684 hospitals with a principal discharge diagnosis of AMI (March 4, 1994 -June 30, 1995). We had 195,832 patients for this analysis after excluding patients less than 65 years old and those of ethnicity other than African American or White. We ascertained use of acute reperfusion, β-blockers, aspirin, and angiotensin converting enzyme inhibitors (ACE-I) among patients who were clinically indicated for therapy. Using multivariable analysis, we adjusted for demographics, severity of illness, and comorbidity.

**Results:** Of the 13,234 African American (AA) patients, 55% were female and 45% were male, and of the 182,598 White patients, 46% were female and 54% were male. AA patients were younger (mean age 72 versus 75, $p<0.05$), more acutely ill (mean APACHE II 9.8 versus 9.2, $p<0.05$), and more likely to be diabetic (94% versus 68%, $p<0.05$), hypertensive (51% versus 38%, $p<0.05$), and have chronic renal insufficiency (23% versus 12%, $p<0.05$). The table below compares the utilization of each therapy. (N is number of patients clinically indicated for each therapy.)

| | | Unadjusted Utilization Rates (%) | | Adjusted Odds Ratio (OR)* | |
|---|---|---|---|---|---|
| Therapy | N | AA | White | OR | 95% CI |
| ACE-I | 19,272 | 66.2 | 59.1 | 1.23 | 1.09-1.38 |
| β–blockers | 42,184 | 31.7 | 35.9 | 0.83 | 0.77-0.89 |
| Aspirin | 100,239 | 84.2 | 86.1 | 0.91 | 0.84-0.98 |
| Reperfusion | 26,575 | 46.7 | 58.1 | 0.66 | 0.59-0.74 |

*receipt of therapy for African American patients compared to White patients.

**Conclusions:** We found less use of all therapies for African American patients with AMI except for ACE inhibitors, where the reverse was true. Performance rates for both races show ample room for improvement. This was so even when considering only patients clinically indicated for therapy and after adjusting for clinically important covariates in this national data set.

**BREAST CANCER RISK PERCEPTION AND USE OF POSTMENOPAUSAL HORMONE REPLACEMENT THERAPY**

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**BACKGROUND:** Postmenopausal hormone replacement therapy (HRT) has been shown to decrease the risk of coronary heart disease (CHD) and osteoporosis, but increase the risk of breast cancer (BCA). While only 24% of postmenopausal women in the US take HRT and fear of BCA is commonly cited as a reason for refusal, the relationship between HRT use and BCA risk perception is not known.

**OBJECTIVES:** To assess relationship between breast cancer risk perception and use of hormone replacement therapy.

**DESIGN:** Cross-sectional mailed survey.

**PARTICIPANTS:** 400 randomly selected postmenopausal women from a general internal medicine practice

**MAIN RESULTS:** From the 268 women (67%) who returned surveys, 189 were postmenopausal. 70 women (37%) were currently using HRT and 21 (11%) had previously used HRT. Mean perceived lifetime risk of BCA was 31% (+/- 21%) – substantially higher than mean predicted lifetime risk of 9% (+/- 4%). However, 80 women (44%) thought their BCA risk was lower than the average woman's, while only 24 (13%) thought it was higher. 59 women (33%) thought HRT increased the risk of BCA, 22 (12%) thought it did not and 100 (55%) were unsure. After multivariate adjustment, current use of HRT was inversely associated with age (OR 0.96 for each 1 year increase, 95% CI 0.94-0.98), and positively associated with Caucasian race (OR 2.73, 95% CI 1.40-5.32). Use of HRT was not associated with quantitative or qualitative measures of breast cancer risk perception, perceived severity of breast cancer, or belief that HRT increases the risk of BCA.

**CONCLUSIONS:** Breast cancer risk perception does not predict decisions about HRT. Use of HRT is associated with race and age. More work is needed to understand the causes of these associations and the reasons why many women do not take HRT.

**BARRIERS TO INFLUENZA VACCINATION IN AN INNER CITY POPULATION: MISTRUST AND MISPERCEPTIONS**

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**BACKGROUND:** Influenza remains a serious threat to the health of the US elderly population. Although vaccination reduces influenza mortality by over 50%, over a third of elderly Americans are not vaccinated each year. Mistrust of the health care system is often cited as a barrier to medical care and research participation among African-Americans. The influence of mistrust on acceptance of influenza vaccination in an inner city population is unknown.

**OBJECTIVES:** To assess the role of mistrust of vaccine contents and other factors in the use of influenza vaccination among an inner city, predominantly African-American, low income population.

**DESIGN:** Cross-sectional telephone survey.

**PARTICIPANTS:** 850 randomly selected community-dwelling individuals 65 years of age or older

**MAIN RESULTS:** From the 486 individuals (70.7%) successfully interviewed, 304 (62.5%) reported influenza vaccination in the previous year. 97 individuals (20%) were concerned that the shot contained something other than influenza vaccination that they did not know about. After multivariate adjustment, mistrust of vaccine contents was inversely associated with vaccine receipt (OR 0.49, 95% CI 0.26-0.91). Receipt of influenza vaccination was inversely associated with belief that vaccination is inconvenient (OR 0.14, 95% CI 0.05-0.36), belief that vaccination is painful (OR 0.21, 95% CI 0.08-0.54) and previous side effects (OR 0.33, 95% CI 0.18-0.60) and positively associated with physician recommendation (OR 3.22, 95% CI 1.76-5.93).

**CONCLUSIONS:** Mistrust of vaccine contents impedes acceptance of influenza vaccination in an urban, predominantly African-American population. Programs to increase vaccination rates in the inner city should address mistrust of vaccination, as well as convenience, discomfort, side-effects and failure of health care providers to recommend vaccination.

ADHERENCE WITH ANTIRETROVIRAL THERAPY IN HIV-INFECTED DRUG USERS. JH Arnsten, RW Grant, PA Demas, MN Gourevitch, EE Schoenbaum, Department of Medicine, Department of Epidemiology and Social Medicine, Montefiore Medical Center, Bronx, NY.

Objective: To describe adherence with antiretroviral therapy (ART) in HIV-infected drug users and determine the impact of adherence on HIV viral load.

Methods: Patients (pts) recruited from a prospective longitudinal study of current and former drug users are given medication event monitoring devices (MEMS) for each antiretroviral. MEMS devices are electronic bottle caps that record the time and date of each opening as a presumptive dose. Monthly interviews include adherence assessments by MEMS and self-report, collection of psychosocial and drug use data, and quantification of viral load.

Results: To date, 53 pts have enrolled and used 122 MEMS devices for 3655 patient-days. Pts are taking a mean of 2.3 ART medicines. Their mean age is 45; pts are 62% male, 66% Hispanic, and 23% Black; 83% are on methadone and 100% are insured by Medicaid. By self-report, pts took 83% of all prescribed doses in the day preceding the interview and 84% in the preceding week. By MEMS device, pts took a mean of 54% of all prescribed doses during the monitored period (median 74.3 days); 23% of pts took >80% of all doses, and 27% took <20%. Pts took all doses on time (within 25% of prescribed interval) on 26% of monitored days. Overall MEMS-adherence (mean % doses taken/doses prescribed) was significantly lower for women (38%) v. men (63%); for active drug users (32%) v. former drug users (61%); and for pts with 2 or more HIV-related symptoms (36%) v. asymptomatic patients (68%) (all $p<0.01$). In a linear regression model adjusted for CD4 count and sociodemographics (age, race, marital status, SSI), only HIV symptoms remained significantly associated ($p<0.01$) with poorer MEMS-adherence. Viral load and CD4 count were more strongly correlated with MEMS-adherence than with self-report adherence (see table).

| | MEMS | p-value | Self-report | p-value |
|---|---|---|---|---|
| Viral load < 10,000 | 62% | 0.001 | 88% | 0.06 |
| Viral load > 10,000 | 26% | | 73% | |
| CD4 > 200 | 61% | NS | 87% | NS |
| CD4 < 200 | 54% | | 84% | |

Conclusions: Among HIV-infected drug users, adherence rates by MEMS and self-report are widely divergent and only MEMS-adherence is associated with viral load. Women, active drug users, and symptomatic pts are less adherent; symptoms are the strongest predictor of poor adherence. The divergence of MEMS and self-report is consistent with other populations. These results strongly support the need for interventions to improve adherence to ART.